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

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Summary
Background Current management of malnutrition can include prescribed oral nutritional supplements (ONS); however, there is uncertainty whether these supplements are effective in people who are older (≥65 years) and frail. We assessed the effectiveness, cost-effectiveness, and adherence and acceptability of ONS in frail older people who are malnourished or at risk of malnutrition.

Methods In this systematic review and meta-analysis, five bibliographic databases (MEDLINE, EMBASE, Cochrane Library, Scopus, and CINAHL) and grey literature sources were searched from inception to Sept 13, 2021, to identify studies assessing the effectiveness and cost-effectiveness of ONS (with or without other dietary interventions) in frail older people who are malnourished or at risk of malnutrition. Multiple reviewers independently did study screening, data extraction, and risk of bias assessment. Quality was assessed using version 1.0 of the Cochrane risk of bias tool for randomised controlled trials (RCTs), and the BMJ Drummond checklist was used to assess the quality of the included cost-effectiveness study. A meta-analysis was done for the effectiveness review; for the other reviews, a narrative synthesis approach was used. This systematic review and meta-analysis was registered on PROSPERO, CRD42020170906.

Findings Of 8492 records retrieved and screened, we included 11 RCTs involving 822 participants, six of which were fully or partly funded by industry. For the majority of the outcomes for which meta-analyses were possible (11/12), Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) assessments suggested that the evidence was of very low certainty. Results suggested that ONS might have a slightly positive effect on energy (kcal) intake (standardised mean difference 1·02 [95% CI 0·15 to 1·88]; P=87%; four studies), protein intake (standardised mean difference 1·67 [–0·03 to 3·37; P=97%; four studies), and mobility (mean difference 0·03 [0·02 to 0·04]; P=60%; four studies), compared with standard care. Narrative syntheses suggested that the effect of ONS on quality of life, compared with standard care, was mixed. In the identified studies, there was very little information related to active components, determinants, or acceptability of interventions. One economic evaluation, done in a care home setting, showed that ONS could be cost-effective.

Interpretation We found little evidence of ONS reducing malnutrition or its associated adverse outcomes in older people who are frail. High-quality, non-industry-funded, adequately powered studies reporting on short-term and long-term health outcomes, determinants, and participant characteristics are needed.

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Research in context

Evidence before this study
Malnutrition (defined here as undernutrition) is common in frail older adults (≥65 years). One component of nutritional support for managing malnutrition is oral nutritional supplements (ONS). Systematic reviews have shown that ONS can improve outcomes related to malnutrition. However, the evidence base assessing the clinical effectiveness and cost-effectiveness of ONS among frail older people is inconclusive. Before commencing this study, we searched MEDLINE, Google Scholar, and PROSPERO to identify existing or planned English-language systematic and non-systematic reviews detailing the relationship between ONS and health outcomes in older adults, from inception to Feb 1, 2020. Search terms included “ONS” AND “malnutrition”.

Systematic reviews of the effectiveness of ONS have focused on adults more generally (including disease-related malnutrition), or on specific comorbidities. Systematic reviews that have reported the cost-effectiveness of ONS in managing malnutrition have focused on adults and children. To our knowledge, we identified no studies that assessed the effectiveness and cost-effectiveness of ONS in frail older people who are malnourished or at risk of malnutrition.

Added value of this study
This systematic review and meta-analysis aimed to assess the evidence base for ONS among frail older adults who are malnourished or at risk of malnutrition. This important and growing population is at high risk of adverse outcomes from malnutrition, and this study is, to our knowledge, the first to appraise the evidence base of existing studies. We identified 11 studies (from 16 articles) encompassing 822 frail older adults. Most studies assessed ONS effectiveness and adherence and acceptability, with only a single study reporting on cost-effectiveness. Meta-analysis indicated ONS might have a slightly positive effect on energy (kcal) intake (standardised mean difference 1.02 [95% CI 0.15 to 1.88]; I²=87%; four studies), protein intake (standardised mean difference 1.67 [−0.03 to 3.37]; I²=97%; four studies), and mobility (mean difference 0.03 [0.02 to 0.04]; I²=0%; four studies), compared with standard care. The evidence was of very low certainty.

Implications of all the available evidence
Evidence was not available to support firm conclusions on the effectiveness and cost-effectiveness of ONS in frail older adults who are malnourished or at risk of malnutrition. Further adequately powered primary studies that report on short-term and long-term health outcomes, as well as assessing the determinants and participant characteristics that could help in providing an understanding of specific groups for which ONS might be more (or less) effective, are needed. There is also a need for studies to compare ONS with other potentially acceptable dietary interventions, such as food fortification and dietary advice.

Methods
Search strategy and selection criteria
This systematic review and meta-analysis was registered on PROSPERO (CRD42020170906) and was reported according to PRISMA guidelines.4 A single search was done for the different aspects that the systematic review encompassed—namely, effectiveness, cost-effectiveness, and adherence and acceptability. This approach meant that the yield of studies from a single search strategy was apportioned to the different aspects. A more detailed description of the methods and results can be found in the accompanying report.35 Details from the protocol can be found online.

Five electronic databases were searched from inception to Sept 13, 2021 (MEDLINE, EMBASE, Cochrane Library,
Scopus, and CINAHL; appendix pp 1–4); grey literature searches were also done (eg, professional bodies, charitable organisations, conferences and theses, and guidelines). Only English-language publications were considered. The databases were searched using key words and Medical Subject Headings (ie, MeSH) developed by information specialists (CR and HO’K). Backwards and forwards citation chaining of included studies was done, and relevant systematic reviews were assessed by the review team (OA, EJ, and KHT) against the review inclusion criteria.

The inclusion criteria for the review in terms of Population, Intervention, Comparison, Outcome, and Study design were determined a priori. The population encompassed participants who were aged 65 years and older, able to swallow, malnourished or at risk of malnutrition, and considered to be frail. Frailty was defined using any standardised measure (eg, Fried frailty phenotype, frailty index, or the cumulative deficit model). In a change from protocol, and after discussion with clinical members of the systematic 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. Malnutrition or risk of malnutrition was defined by standardised tools (eg, Malnutrition Universal Screening Tool, Mini Nutritional Assessment [MNA], or MNA-Short Form). All settings were considered (eg, community, care homes, and hospitals).

Eligible interventions comprised any form of prescribed ONS, with or without dietary advice or counselling. ONS were defined as multinutrient products containing macronutrients and micronutrients, designed to increase energy and nutrient intake of individuals with or at risk of malnutrition. We included studies that assessed an eligible intervention against any comparator intervention.

The outcomes varied across the three different reviews. The following outcomes were eligible for the effectiveness review: malnutrition, outcomes associated with malnutrition (eg, wound healing, hospital admissions, reduction in infections, falls, grip strength, and Activities of Daily Living [ADLs]), functional status, change in frailty status, quality of life, mortality, morbidity, and adverse events. For the review concerning adherence and acceptability, the eligible outcomes included barriers and facilitators to the use of ONS (eg, determinants such as socioeconomic factors, living arrangements, social support, and mode of ONS administration, and specific groups of older adults), treatment persistence, adherence and acceptance, and the role of carers in delivering the intervention.

For the cost-effectiveness review, the outcomes were total costs, summary health outcomes, incremental cost-effectiveness ratios, and resource use.

We included parallel-arm, cross-over, and cluster-randomised controlled trials (RCTs), as well as prospective, comparative non-RCTs (eg, cohort and case-control studies). Mixed-methods and qualitative studies were also eligible for review of adherence and acceptability.

Results from the database searches were imported into EndNote® and duplicates were removed. Screening was managed in Covidence and completed independently by three reviewers (OA, EJ, and CM). When multiple publications reported data from the same study, decisions on which publications to include were based on sample size, date of publication, as some studies presented preliminary results, and outcomes (appendix p 5).

Data analysis

Data extraction and quality appraisal were done by one reviewer (OA or EJ) and checked in full by a second reviewer (OA or EJ as appropriate). Version 1.0 of the Cochrane risk of bias tool was used to assess RCTs. The quality of the included cost-effectiveness studies was assessed with the BMJ Drummond checklist (36-point checklist). Any discrepancies in screening, extraction, and quality appraisal were resolved through discussion between reviewers and the project lead (SER).

We conducted meta-analyses using a random-effects model to compare ONS with standard care, if at least two studies compared an outcome and if required data were reported or calculable (ie, mean and SD for continuous variables, number of events, and sample size for binary variables). An inverse variance random-effects model was used for continuous outcomes, and a Mantel-Haenszel random-effects model was used for binary outcomes. For binary outcomes, 0·5 was added to the number of events and 1 to the total. In the primary analysis, the DerSimonian and Laird estimator for between-study variance and the variance of the pooled outcomes. For binary outcomes, 0·5 was added to the number of events and 1 to the total. In the primary analysis, the DerSimonian and Laird estimator for between-study variance and the variance of the pooled effect estimator was used. Meta analyses were conducted in R (version 4.2.1). In the sensitivity analysis, the Hartung-Knapp estimator for the variance of the pooled effect estimator was used for both continuous and binary outcomes, and the restricted maximum likelihood estimator was used for the between-study variance for continuous outcomes.

The degree of heterogeneity was estimated using the $I^2$ statistic, and the p value for the χ² statistic was used to measure the strength of evidence for heterogeneity. We calculated the risk ratio (RR) for binary outcomes, the mean difference (MD) when continuous outcomes were measured on the same scale across studies, and the standardised mean difference (SMD) for continuous outcomes not measured using the same tool across studies, as well as their corresponding 95% CIs. Change from baseline scores was calculated for continuous outcomes. Further details on the methods are provided in the appendix (pp 6–7). SMDs were calculated using Hedges’ adjusted g. Narrative synthesis methods were used to report outcomes with insufficient data to include
in a meta-analysis, and to integrate the narrative and meta-analysis data. Synthesis involved broadly splitting the data into three key categories, which correspond to the period over which the outcomes might be expected to induce a noticeable change (outcomes relating to nutritional intake and visceral protein, body composition outcomes, and those relating to longer term outcomes). Adherence and acceptability is then presented, alongside the cost-effectiveness results.

We used Grading of Recommendations, Assessment, Development and Evaluation (GRADE) to assess the overall certainty of evidence. All outcomes were independently assessed by two reviewers (OA and EJ). GRADE assessments for each outcome can be found in the appendix (pp 8–9).

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Database searches identified 11,753 records, with an additional 659 records identified from grey literature sources. A further 64 additional records were identified from citation chaining (figure 1). 621 articles were screened at full text (details relating to exclusion are provided in the appendix [pp 10–39]). 16 records met the inclusion criteria (appendix p 44); four of these records reported duplicate data and were not used for the effectiveness or adherence and acceptability review but were used to quality appraise the studies where appropriate (appendix p 5). Included articles were published between the years 2000 and 2018. 11 studies were included in the effectiveness review and in the adherence and acceptability review,46,48–57 of which ten articles were included in the meta-analysis (Otten and colleagues’ study53 was excluded from the meta-analysis because they compared dietary counselling with ONS and dietary counselling, whereas this meta-analysis included only studies comparing ONS with standard care).46,48–52,54–57 One study47 was included in the cost-effectiveness review, which was based on an RCT included in the effectiveness review.46

All 11 studies included in the effectiveness review were RCTs; one study was a cross-over RCT,46 four studies were multiarm RCTs,46,52,55,57 and the remaining six studies used a parallel group design with two groups.46,50,51,54 822 people were recruited across the 11 studies. The smallest study56 recruited 39 participants, whereas the largest recruited 104 participants. Further characteristics of the 11 included studies are shown in the table. One study48 included in the effectiveness review (based in nursing or residential homes in the UK) had conducted a corresponding cost-effectiveness analysis.47 Two studies took place in Australia,46,52 two in France,46,57 one in Germany,46,53 two in Sweden,46,55 and one each in the UK,46 Russia,46 Canada,46 and Taiwan.51 Five studies were set in nursing or residential homes;46,50,51,55,57 of these, four studies took place in multiple nursing homes.46,50,51,55 We acknowledge that definitions of nursing or residential homes vary internationally; however, our groupings were purely for descriptive purposes. Two further studies were set in the community,46,53 and three were set in hospital.46,50,52 One study stated it was conducted after discharge from hospital.46 Reporting on intervention duration and follow-up was often inadequate and included insufficient detail. Of the 11 studies identified,
six studies (55%) were either fully (n=4), or partly funded by industry (n=3). Four studies were funded by alternative sources and two studies did not include details of funding or conflicts of interest.

Five (45%) of the 11 included RCTs were judged to be at low risk of selection bias,\textsuperscript{46,49–51,54,57} allocation concealment,\textsuperscript{46,49,52,55,57} detection bias,\textsuperscript{46,49,52,54,57} and selective reporting bias.\textsuperscript{46,49,52,54,57} Of the 11 RCTs, four (36%)\textsuperscript{46,49,56,57} were considered to be at high risk of attrition bias and six (64%)\textsuperscript{48,52,53,55–57} were judged to be at an unclear risk of other bias. Risk of bias assessments are summarised in the appendix (p 40).

We did not identify any studies that reported data for the effectiveness of ONS on frailty, wound health, falls, or admission to long-term care. Seven studies reported on the effects of ONS on nutritional intake and visceral protein outcomes,\textsuperscript{46,49–51,54–56} including energy (kcal), intake, protein intake, and serum albumin concentration (figure 2 A–C).

ONS appeared to have a positive effect on energy intake (SMD 1.02 [95% CI 0.15 to 1.88]; \textit{P}=87%; four studies; very low certainty evidence) and a slightly positive effect on protein intake compared with standard care (SMD 1.67 [–0.03 to 3.37]; \textit{P}=97%; four studies; very low certainty evidence). There was evidence of substantial heterogeneity in both analyses. These estimates were not significant in sensitivity analyses (appendix p 41). Five studies suggested no effect of ONS versus standard care on serum albumin concentrations, with evidence of substantial heterogeneity (MD 1.48 [95% CI –0.44 to 3.41]; \textit{P}=95%; very low certainty evidence). CIs were very wide in primary analyses, and were even wider using the Hartung-Knapp method in sensitivity analyses.

Eight studies reported on the effects of ONS on body composition,\textsuperscript{46,49–51,54,57} including body weight, BMI, arm circumference (a proxy of BMI), and fat-free muscle mass (figure 2 D–F). We were unable to produce a meta-analysis for arm circumference. There was no evidence of a pooled effect between ONS and standard care in terms of body weight in kg (MD 1.31 [95% CI –0.05 to 2.66]; \textit{P}=74%; five studies; very low certainty evidence), or change from baseline in BMI (MD 0.54 [–0.03 to 1.11]; \textit{P}=62%; very low certainty evidence), with evidence of moderate heterogeneity in both analyses. Three studies suggested an inconsistent effect of ONS on fat-free muscle mass compared with standard care (SMD 0.23 [95% CI –0.24 to 0.69]; \textit{P}=58%; low certainty evidence). One study,\textsuperscript{51} with an unclear risk of bias for random sequence generation and allocation concealment, reported on the effect of ONS versus standard care on arm circumference, reporting a mean change of –0.3 cm in the intervention group and –0.8 cm in the control group.

Eight studies reported data on the effect of ONS on longer-term outcomes related to malnutrition.\textsuperscript{46,48–50,52,55,57} Meta-analyses were possible for ADL, grip strength, MNA score, mobility, hospitalisation, and mortality, but it was not possible to meta-analyse quality of life outcomes because of little comparable data across the studies. Forest plots are presented in figure 3. Compared with standard care, there was no significant association between ONS and the ability to undertake ADLs (SMD 0.30 [95% CI –0.69 to 1.29]; \textit{P}=89%; three studies; very low certainty evidence). There was no evidence of an effect of ONS compared with standard care on change in grip strength, although there was evidence of moderate heterogeneity (SMD 0.17 [95% CI –0.23 to 0.58]; \textit{P}=53%; five studies; very low certainty evidence). There was also no evidence of an effect of ONS on hospitalisations (RR 0.97 [95% CI 0.46 to 2.04]; \textit{P}=0%; five studies; very low certainty evidence), change in MNA score (SMD –0.36 [–0.81 to 0.09]; \textit{P}=6%; two studies; very low certainty evidence), or mortality (RR 0.93 [0.28 to 3.06]; \textit{P}=0%; four studies; very low certainty evidence). However, there was evidence to suggest that ONS might result in a positive effect on mobility compared with standard care, with no evidence of heterogeneity (MD 0.03 [0.02 to 0.04]; \textit{P}=0%; four studies; very low certainty evidence). Estimates for mobility were not significant in sensitivity analyses (appendix p 42).

Four studies reported on the effect of ONS on quality of life\textsuperscript{48,52–54} of life scores, whereas two reported data from psychological and physical subdomains of quality of life tools.\textsuperscript{52,54} The results across studies reporting on the effect of ONS on overall quality of life and physical function domains were mixed, though one\textsuperscript{52} out of two studies\textsuperscript{52,54} reported a positive effect of ONS on psychological aspects of quality of life compared with standard care.

One study reported that, at 12 months, deep infections engaging the hip joints were reported by two (12%) of 17 people in the control group but not in the intervention groups,\textsuperscript{55} although more urinary tract infections were reported in the intervention groups compared with control. This study had a low risk of bias across four of the seven domains reported in the risk of bias assessment.

Three studies reported on adverse events or withdrawal from treatment, but a meta-analysis was not possible.\textsuperscript{46,52,56} In general, across these studies, slightly fewer participants taking ONS had adverse events compared with the control group.

Outcomes related to the reduction in infections and adverse events were synthesised narratively. These outcomes were typically poorly reported and showed mixed effects. No evidence for changes in self-reported mobility, improvement in frailty, morbidity, wound healing, reduction in falls, and admission to long-term care was identified in the 11 primary studies.

With regards to the adherence and acceptability review, despite an inclusive search strategy, little information was found in the included studies on barriers and facilitators, including determinants that can influence the uptake of ONS. No studies assessed the effectiveness of ONS in specific groups of older adults. No studies
| Country          | Study design | Setting                                      | Number enrolled (withdrawals, % range or number of people)* | Duration of intervention (ONS) and follow-up | Intervention                                                                                                           | Outcomes                                                                 | Study funding source/conflict of interest                                                                 |
|-----------------|--------------|----------------------------------------------|-------------------------------------------------------------|---------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| Parsons et al   | UK           | RCT Nursing home: care homes in Hampshire    | 104 (NR)                                                   | Treatment duration: 12 weeks; follow-up duration: NR | ONS (range of Nutricia products available to choose from) (n=53) vs dietary advice (specially designed diet sheet; n=51) | Body weight, change in nutritional intake, hospitalisations, mortality, and quality of life | An unrestricted educational grant from Nutricia                                                              |
| Lauque et al    | 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; n=19 participants at risk of malnutrition) vs ONS (Clinutren; n=28 participants who were malnourished, group not included in meta-analysis) vs no supplementation (n=19 participants who were well nourished, group not included in meta-analysis) vs no supplements (n=22 participants at risk of malnutrition) | Body weight, BMI, energy intake (kcal), protein intake, change in malnutrition risk, handgrip (or other muscle) strength, and mortality | NR                                                                                                                  |
| Luo et al       | Russia       | RCT Hospital                                  | 55 (4/5 persons)                                          | Treatment duration: 28 days; follow-up duration: NR | ONS (Ensure TwoCal) plus standard hospital food (n=26) vs standard care, including standard 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) |
| Cameron et al   | 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 and 4 months | Liquid high-calorie, high-protein supplementation (Novasource/Sustagen Hospital PHS) and diet of choice (n=22) vs standard care (high protein diet with high protein milk; n=21) | Body weight, fat-free muscle mass, BMI, 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 |
| Lee et al, (2013)| Taiwan      | RCT Nursing home: geriatric nursing home     | 92 (NR)                                                   | Treatment duration: 24 weeks; follow-up duration: 24 weeks, 1 year | Liquid ONS and all essential micronutrients taken as an afternoon snack (n=47) vs NR (assumed standard care; n=45) | Body weight, mid-arm circumference, fat-free muscle mass, BMI, and other indicators of nutritional status | Asia University                                                                                                       |
| Miller et al    | 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) vs exercise (resistance training; n=25; group not included in meta-analysis) vs Liquid ONS and exercise (n=24; group not included in meta-analysis) vs standard care (general nutrition and exercise advice, usual dietetic and physiotherapy care, and onward transfer; n=26) | Body weight, BMI, hospitalisations, gait speed, handgrip (or other muscle) strength, mortality, and quality of life | National Health and Medical Research Council Public Health Postgraduate Research Scholarship, Flinders University-Industry Collaborative Research Grant, and Nutricia Australia (no details given of the role of industry partner in research) |
| Otten et al     | Germany      | RCT After hospital discharge                 | 71 (NR)                                                    | Treatment duration: 1 month; follow-up duration: NR | Dietary counselling (n=NR) vs dietary counselling plus ONS (n=NR) | Quality of life                                                                                                         | NR                                                                                                                    |
| Payette et al   | Canada       | RCT Community: home                          | 83 (9–9.8%)                                               | Treatment duration: 16 weeks; follow-up duration: NR | Liquid ONS (Ensure or Ensure Plus; n=41) vs standard care (n=41) | Body weight, fat-free muscle mass, energy intake (kcal), protein, TUG test, handgrip (or other muscle) strength, and quality of life | Abbott Laboratories (no details given of the role of industry partner in research) |

(Table continues on next page)
assessed determinants for specific groups. Typically, the data presented in studies were based on informal observations by the research team. Compliance with ONS was reported in five studies. One study reported on compliance narratively with no supporting data, making it difficult to draw any firm conclusions regarding how well participants adhered to ONS. Methods for measuring and reporting compliance across studies were heterogeneous. The lowest level of compliance to ONS was reported by Payette and colleagues, which assessed adherence defined by supplement use (number of remaining ONS cans) and total energy intake; 23 (55%) of 42 participants were compliant at 16 weeks. The highest compliance was possible to directly compare compliance to ONS to 100% of recommended intake. Van Wymelbeke and colleagues’ study was the only included study in which it was possible to directly compare compliance to ONS with that to a second intervention (protein-and-energy-enriched brioche). At 90 days, the study reported that 74% of 17 participants in the ONS group consumed ONS, compared with 83% of 29 participants in the group who consumed brioche. A summary of characteristics of the included studies and participants, evidence quality, and findings is presented in figure 4.

The nature of the interventions in the included studies, such as the flavour and texture, was closely examined to understand how the delivery of the intervention could affect the effectiveness of the intervention; however, reporting on the nature of the interventions varied across studies. Five studies reported on the flavour of ONS.
Figure 2: Forest plots of nutritional intakes and visceral protein intakes and body composition outcomes
IV=inverse variance. ONS=oral nutritional supplement. SC=standard care. SMD=standard mean difference.
Figure 3: Forest plots for longer term outcomes

ADL=Activities of Daily Living. IV=inverse variance. ONS=oral nutritional supplement. SC=standard care. SMD=standard mean difference.
The flavours reported ranged between sweet and savoury, with strawberry as the most common flavour available across all five studies.46,48,54,56,57 No association between the variation in the flavours of the interventions and adherence was reported in these five studies. One study47 with an economic evaluation was included in the systematic review of cost-effectiveness; the study was conducted in a care home setting. The study was judged to be well conducted (appendix p 43).47 The study found that ONS were associated with greater benefits (quality-adjusted life years [QALYs]) and with higher costs than the comparator (dietary advice).47 The estimated incremental cost-effectiveness ratio (ICER) for ONS was £10,941 per QALY. This ratio is less than one of the cost-effectiveness thresholds used by the National Institute of Health and Care Excellence—£20,000 per QALY—indicating ONS was cost-effective at that threshold. There was moderate certainty that the ICER was less than £20,000 per QALY, with a 0·83 probability of being cost-effective.47

Discussion
This systematic review and meta-analysis examined the effectiveness of ONS in frail older people who are malnourished or at risk of malnutrition. There were 11 primary studies identified in the effectiveness review. Modest improvements in energy, protein intake, and mobility were observed with ONS compared with standard care, although the quality of evidence was very poor. Estimates for energy and protein intake were not statistically significant in sensitivity analyses. The 95% CIs of the pooled effects were very wide, with high heterogeneity, indicating a wide range in possible effect sizes, which might vary by setting, intervention type, or
systematically reported in the identified studies. Although influence compliance and uptake of ONS, were not Furthermore, types or characteristics of ONS, which can resilience, and little knowledge about food) and personal disability), psychosocial aspects (eg, social support, ageing (eg, loss of appetite, poor taste and smell, and psychosocial aspects (eg, social support, resilience, and little knowledge about food) and personal resources (eg, poverty and inability to shop for food).26–29

With the small evidence base, it was not possible to assess the differential impact of ONS among frail older adults. Furthermore, types or characteristics of ONS, which can influence compliance and uptake of ONS, were not systematically reported in the identified studies. Although some studies in our review reported on compliance, there was considerable between-study heterogeneity in how compliance was determined and reported, which made it difficult to draw firm conclusions. A previous systematic review,29 suggested that mean compliance with ONS was 78%, with lower compliance in hospital compared with community settings (67% vs 81%). Previous research has highlighted that age-related changes in taste can contribute to the dislike of ONS.25 Research has shown that the thickness of the ONS also has an important role in oral-sensory stimulation and satiety and can influence compliance to ONS.26 Few qualitative findings on barriers to the use of ONS from the perspectives of frail older adults were found in our analysis.

One study was identified in the cost-effectiveness review. The reasonably well conducted economic evaluation concluded that ONS might 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.

This systematic review and meta-analysis has many strengths. Our search strategy was broad. All screening, data extraction, and quality assessments were done in duplicate or checked in full by a second reviewer to minimise human error. We also included a range of outcomes to ensure the effects of ONS could be investigated across a range of health outcomes, including both those hypothesised to respond relatively quickly to ONS (eg, energy intake and protein) and those which might be affected over a longer period (eg, hospitalisations, morbidity, and mortality). 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.

There are, however, some limitations to this systematic review and meta-analysis and to the evidence base more widely. Only studies published in English were included, which may have excluded some potentially eligible studies. We also deviated from our original protocol by refining the eligibility criteria with regards to frailty. In the original protocol, we specified that frailty needed to be defined according to a standardised measure, such as the Fried frailty phenotype. However, upon screening the search results we found that very few study populations were described as frail using standardised measures. Therefore, we decided to expand the eligibility criteria for frailty by utilising proxy criteria.

Our review identified only a small evidence base related to a population of frail older adults who were either malnourished or at risk of malnutrition. Most studies were based on small samples and the duration of intervention reported was typically 3 months or less. The effectiveness of ONS on malnutrition-related outcomes (eg, grip strength, ADL, and hospitalisation) is difficult to establish over these relatively short durations. Furthermore, the dose of ONS typically varied across the studies, which could add to the inconsistency observed. This important and growing population of frail older adults, nonetheless, is at high risk of adverse outcomes from malnutrition, and there is little evidence on the effectiveness of ONS to treat malnutrition risk. Fewer than 10 studies were included for any one outcome in the meta-analysis. Few included studies and the variation in estimates across studies meant that effect sizes and heterogeneity could not be estimated precisely. Small sample sizes and sparse data for binary outcomes could introduce bias.58–62 These small sample issues are probably less important than the issue of heterogeneity. Moreover, funnel plots could not be used to assess publication bias, and sources of heterogeneity could not be assessed either. Many of the studies were not adequately randomised and had incomplete outcome data, which has implications for the reliability of these studies. Additionally, measures such as serum albumin concentration in this age group are not necessarily a good indicator of protein status. Many of the studies had some degree of industry funding and the role of funders in the study was not always clear. Given the insufficient information on the role of funders, the potential limitation of conflicts of interest in reporting findings cannot be ruled out given the insufficient clarity on independent research.

There were also limitations associated with evaluating cost-effectiveness. There was very little evidence identified in systematic review on health-care resources and outcomes that affect quality of life, and this limited...
conclusions on cost-effectiveness that could be drawn from this evidence. There were no economic evaluations identified that were conducted in settings other than care homes.

This systematic review and meta-analysis identified little evidence for the effectiveness of ONS in reducing malnutrition or its adverse outcomes in frail older adults. It is possible that ONS had a modest positive effect on energy intake and mobility in frail older adults. The limited cost-effectiveness evidence indicated that ONS might be cost-effective in a care home setting. As there was only one cost-effectiveness study, it remains unknown how the cost-effectiveness of ONS varies across population subgroups defined by, for example, age, degree of functional independence, and BMI.

Evidence was not available to support firm conclusions on the effectiveness and cost-effectiveness of ONS in frail older adults. Further adequately powered primary studies that report on short-term and long-term health outcomes, along with assessing the determinants that could help to provide an understanding of specific groups for which ONS might be more (or less) effective, are needed. Qualitative research studies done in a range of settings (eg, community, hospital, and social care) would further help to provide an understanding of issues related to acceptability of ONS. There is also a need for studies to compare ONS with other potentially acceptable dietary interventions, such as food fortification and dietary advice.

Contributors
KHT and OA contributed to methodology, formal analysis, investigation, writing of the original draft, and visualisation. SR and EJ contributed to methodology, formal analysis, investigation, and writing of the original draft. LT contributed to conceptualisation, methodology, formal analysis, investigation, writing of the original draft, visualisation, and funding acquisition. CM and AR contributed to methodology, investigation, and writing of the original draft. TS and WM contributed to investigation and writing of the original draft. CR and HO’K contributed to methodology and writing of the original draft. BH contributed to conceptualisation, methodology, writing of the original draft, and funding acquisition. CTM contributed to conceptualisation, methodology, formal analysis, writing of the original draft, and funding acquisition. SER contributed to conceptualisation, methodology, formal analysis, investigation, writing of the original draft, supervision, and funding acquisition. KHT, SR, and SER have had access to and verified the data.

Declaration of interests
DC was a member of a researcher-led panel for the National Institute for Health Research (NIHR) Health and Social Care Delivery Research (HS&DR) and is currently a member of HS&DR Funding Committee. KHT, SR, OA, EJ, LT, CM, TS, CR, HO’K, WM, AR, BH, CTM, and SER declare no competing interests.

Data sharing
Extracted data are available from the corresponding author on reasonable request.

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