# Nutritional supplementation for hip fracture aftercare in older people (Review)

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 1

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[Intervention Review]

# Nutritional supplementation for hip fracture aftercare in older people

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**Editorial group:** Cochrane Bone, Joint and Muscle Trauma Group.
**Publication status and date:** Edited (conclusions changed), published in Issue 1, 2010.
**Review content assessed as up-to-date:** 28 February 2009.

**Citation:** Avenell A, Handoll HHG. Nutritional supplementation for hip fracture aftercare in older people. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD001880. DOI: 10.1002/14651858.CD001880.pub5.



## ABSTRACT

### Background

Older people with hip fractures are often malnourished at the time of fracture, and have poor food intake subsequently.

### Objectives

To review the effects of nutritional interventions in older people recovering from hip fracture.

### Search strategy

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (September 2008), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2008, Issue 3), MEDLINE and other major databases (to July 2008).

### Selection criteria

Randomised and quasi-randomised controlled trials of nutritional interventions for people aged over 65 years with hip fracture.

### Data collection and analysis

Both authors independently selected trials, extracted data and assessed trial quality. We pooled data for primary outcomes.

### Main results

Twenty-four randomised trials involving 1940 participants were included. Outcome data were limited and many trials were methodologically flawed. Results from 23 trials are presented here.

Ten trials evaluated oral multinutrient feeds: providing non-protein energy, protein, some vitamins and minerals. Oral feeds had no statistically significant effect on mortality (16/244 versus 21/226; risk ratio (RR) 0.76, 95% confidence interval (CI) 0.42 to 1.37) or 'unfavourable outcome' (combined outcome of mortality and survivors with medical complications) (46/126 versus 41/103; RR 0.76, 95% CI 0.55 to 1.04).

Four heterogenous trials examining nasogastric multinutrient feeding showed no evidence of an effect on mortality (RR 0.99, 95% CI 0.50 to 1.97). Nasogastric feeding was poorly tolerated.

One trial examining nasogastric tube feeding followed by oral feeds found no evidence for an effect on mortality or complications.

One trial of multinutrient intravenous feeding followed by oral supplements found a reduction in participants with complications (RR 0.21, 95% CI 0.10 to 0.46), but not in mortality (RR 0.11, 95% CI 0.01 to 2.00).

Four trials testing increasing protein intake in an oral feed found no evidence for an effect on mortality (RR 1.42, 95% CI 0.85 to 2.37). Protein supplementation may have reduced the number of long term medical complications.

Two trials, testing intravenous vitamin B1 and other water soluble vitamins, or oral 1-alpha-hydroxycholecalciferol (vitamin D) respectively, produced no evidence of effect.

One trial, evaluating dietetic assistants to help with feeding, showed no statistically significant effect on mortality (RR 0.57, 99% CI 0.29 to 1.11).

**Authors' conclusions**

Weak evidence exists for the effectiveness of protein and energy feeds. Adequately sized randomised trials with robust methodology are required. In particular, the role of dietetic assistants, and peripheral venous feeding require further evaluation.

## PLAIN LANGUAGE SUMMARY

**Nutritional supplementation for older people after hip fracture**

Older people with hip fractures are often malnourished at the time of their fracture and many have poor food intake while in hospital. Malnutrition may hinder recovery after hip fracture. We reviewed the effects of nutritional interventions in older people recovering from hip fracture.

The 24 randomised controlled trials included in this review involved 1940 participants. The trials had methodological flaws that may affect the validity of their results. Ten trials examined the use of additional feeds by mouth providing non-protein energy, protein, some vitamins and minerals. Pooled data from these trials found that there may be a possibility of a reduction in 'unfavourable outcome' (combined outcome of mortality and survivors with medical complications), but no effect on mortality.

Four trials examined nasogastric tube feeding, where liquid food is delivered via a tube inserted into the nose and passed down into the stomach, with non-protein energy, protein, some vitamins and minerals. These trials provided very limited data but tube feeding, which was poorly tolerated, did not seem to make a difference to mortality.

One trial found nasogastric tube feeding followed by oral feeds did not seem to affect mortality or complications.

One trial examined giving feed into a vein initially, then by mouth. This did not seem to affect mortality but might reduce complications.

Increasing protein intake in an oral feed was tested in four trials. Protein supplementation may have reduced the number of long term complications, but it did not seem to make a difference to mortality alone.

Two trials examining intravenous vitamin B1 and other water soluble vitamins, or a form of vitamin D given orally, did not alter outcomes.

One unpublished study comparing ornithine alpha-ketoglutarate with an isonitrogenous peptide supplement found very weak evidence of a delay in the onset of complications but not their occurrence.

One trial, evaluating dietetic assistants to help improve nutritional intake found a trend for a reduction in mortality.

Some evidence exists for the effectiveness of protein and energy feeds, but overall the evidence for the effectiveness of nutritional supplementation remains weak. The role of dietetic assistants, and peripheral intravenous feeding require further evaluation. Trials are required which overcome the defects of the reviewed studies, particularly inadequate size and trial methods.

# BACKGROUND

## Description of the condition

Fractures of the proximal femur (hip) are a cause of substantial morbidity and mortality in older people. Nine months after their hip fracture people still have poorer quality of life than age and sex matched controls (Cranney 2005). In industrialised societies, mortality in the year after hip fracture ranges from 12% to 37%, and averages 11% during the first few months after fracture (Lyons 1997). Mortality in the first four months after hip fracture surgery is age dependent: for instance, mortality was reported as 5% in people aged 50 to 69 years compared with 28% in those people aged 90 years or over in the Scottish Hip Fracture Audit Report ( Holt 2008). Many people fail to return to their own homes and previous state of mobility after a hip fracture. Acute hospital costs are substantial, but long term costs in rehabilitation and extra care in the community are even greater (Dolan 1998; Haentjens 2005; Johnell 1997).

Under-nutrition leads to mental apathy, muscle wasting and reduced muscle power, and impaired cardiac function (Keys 1950). All of these will impair mobility and increase the tendency to develop postoperative medical complications (e.g. pneumonia, pressure sores, deep venous thrombosis) and hinder recovery, both in hospital and subsequently (Lennard-Jones 1992). Malnutrition also impairs the immune response, which will enhance the risk of postoperative infections (Lesourd 1997). Poor nutritional status is associated with an increased risk of pressure ulcers after hip fracture (Lindholm 2008).

People with hip fractures, who are more likely to be old and frail, are often malnourished at the time of the fracture (Bachrach 2001a; Bastow 1983a; Lumbers 2001). Social, psychological, physical, economic, medical and cognitive influences may all contribute to the risk of malnutrition. Surveys of dietary intake in people recovering from hip fracture in hospital have recorded suboptimal intakes (Jallut 1990; Lumbers 2001; Nematy 2004; Patterson 1992; Stableforth 1986a).

## Description of the intervention

Examined in this review are nutrition interventions started within the first month after a hip fracture that are aimed to improve the intake of energy, protein, vitamins and minerals, alone or in combination. Nutrition interventions can be provided by various routes: oral (by mouth), enteral (tube feeding into the stomach or small bowel, including percutaneous endoscopic gastrostomy) or parenteral (intravenous and intramuscular). Also considered are interventions that revolve round the administration of nutrition, such as the use of dietetic assistants in hospital.

## How the intervention might work

Making links between nutritional status and fracture recovery is complicated by the fact that markers of dietary protein depletion measured in blood, such as albumin, prealbumin, and transferrin are partly affected by fluid shifts and responses to injury and infection. Nevertheless, associations have been shown between low serum albumin and increased postoperative complications and poorer survival (Foster 1990; Patterson 1992). Another factor which has been implicated is vitamin C which is required for an effective immune response and collagen formation. Low leucocyte vitamin C levels have been associated with the development of pressure sores in hip fracture patients (Brown 1992a; Goode 1992).

More direct markers of nutritional status are anthropometric indices, such as weight in relation to height, triceps skinfold for body fat, and mid-upper arm circumference for muscle and fat mass. People with hip fracture have lower triceps skinfold and mid-upper arm circumference than healthy people in the same age category (Mansell 1990; Nematy 2004). In a study of 744 hip fracture patients, Bastow 1983a found that low triceps skinfold and arm muscle circumference predicted lower calorie intake on the ward and poorer survival after hip fracture. However, in a study of 40 hip fracture patients, Foster et al (Foster 1990) found that low triceps skinfold did not predict survival.

## Why it is important to do this review

The above shows that people with hip fracture are sometimes undernourished, and that poor food intake may occur during routine care, hindering recovery. There is therefore an argument for nutritional supplementation in this group, and consequently a need to evaluate the use of nutrition interventions in this group of people by examining the evidence from relevant randomised controlled trials. This is the sixth update of our Cochrane review first published in 2000, and previously updated in 2006. The previous update (Avenell 2006) continued to point to the insufficiency of the available evidence to draw robust conclusions.

# OBJECTIVES

This review examined the effectiveness, safety and acceptability of nutrition interventions in the care of older people with hip fracture.

We considered comparisons where people with hip fracture, who were randomly allocated a nutrition intervention, including supplements, were compared with those allocated to no intervention or placebo. Where possible, effects were examined according to pre-existing nutritional status: malnourished or not malnourished.

We also considered comparisons between nutrition interventions if these were compared in a randomised controlled trial.

# METHODS

## Criteria for considering studies for this review

### Types of studies

We included all randomised controlled trials (RCTs) of nutritional supplements post hip fracture. Trials that used a quasi-randomisation technique (e.g. allocation by date of birth or hospital record number) were also included. Trials that could not be analysed on an intention-to-treat basis, and those that lacked blinding or use of placebo treatment, were also included.

Studies of nutrition interventions that examined the secondary prevention of osteoporotic fractures after hip fracture were not considered in this review.

### Types of participants

Older people recovering from any type of fracture of the hip were included. It was anticipated that most participants would be over 65 years of age. If the number of younger participants was relatively small, and provided there was adequate randomisation with unbiased distribution of this age group between the intervention and control groups, they were retained. Trials which focused specifically or mainly on younger people, people with multiple trauma or people with pathological fractures (e.g. cancer-related fractures) were excluded. Trials published before 1980 with undefined geriatric populations or with mixed populations with less than five participants with hip fracture in each intervention group were excluded.

Studies reporting results on mixed populations of orthopaedic or other geriatric patients were only included, either if separate data were available from the participants with fracture of the hip, or when contact with the authors resulted in the provision of such data.

The participants studied may have resided in a hospital or in a rehabilitation unit or any location after discharge from either of these facilities.

### Types of interventions

Examined in this review were nutrition interventions aimed to improve the intake of energy, protein, vitamins and minerals, alone or in combination. Nutrition interventions were provided by oral (by mouth), enteral (tube feeding into the stomach or small bowel, including percutaneous endoscopic gastrostomy) or parenteral (intravenous and intramuscular) routes. Interventions include those evaluating the administration of nutrition, such as the use of dietetic assistants. The interventions examined were started within the first month after hip fracture, and given for up to one year. Trials evaluating intravenous fluid administration in the immediate post-operative period for hydration purposes were excluded.

### Types of outcome measures

Information was sought on the following outcomes. As of the update published in Issue 4, 2009, these were split into main outcomes (and further categorised into primary and secondary outcomes) and other outcomes. Additionally, the collection of 'unfavourable outcome' was made explicit.

#### Main outcomes

##### Primary outcomes

- all cause mortality
- morbidity, postoperative complications (e.g. wound infections, pressure sores, deep venous thromboses, respiratory and urinary infections, cardiovascular events)
- 'unfavourable outcome'. This is defined as the number of trial participants who died plus the number of survivors with complications. Alternatively, where these data were unavailable, a slightly different definition (mortality or survivors with a major complication or two or more minor complications) originally presented in Delmi 1990 was accepted.

##### Secondary outcomes

- length of hospital and rehabilitation unit stay
- postoperative functional status (cognitive functioning, mobility and ability to perform activities of daily living)
- the level of care and extent of support required after discharge
- patient perceived quality of life after discharge
- fracture healing
- putative side effects of treatment (e.g. diarrhoea, aspiration pneumonia, specific intravenous line complications)

#### Other outcomes

- patient tolerance of/compliance with nutrition interventions
- carer burden and stress
- economic outcomes
- changes in anthropometric indices, e.g. weight, skinfold thickness, and mid-upper arm circumference
- new fractures

- changes in bone mineral density, assessed by techniques involving radiation, e.g. dual photon absorptiometry, dual energy x-ray absorptiometry, quantitative computed tomography
- changes in nutritional indicators measured in blood, e.g. albumin, transferrin, vitamin and mineral levels, haemoglobin
- changes in functional markers of nutritional status, including delayed cutaneous hypersensitivity (a marker of immune function) and grip strength

## Search methods for identification of studies

### Electronic searches

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (September 2008), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2008, Issue 3), MEDLINE (1966 to July 2008), Nutrition Abstracts and Reviews (1984 to July 2008), EMBASE (1980 to week 32 2008), BIOSIS (1985 to 14 August 2008), CINAHL (1982 to August week 2 2008), and HEALTHSTAR (1975 to March 2002).

In MEDLINE (Ovid) the first two phases of the standard Cochrane search strategy (Higgins 2006) were combined with subject-specific terms. This strategy was modified for use in other databases (*see* Appendix 1 for search strategies). No language restrictions were applied.

We also searched Current Controlled Trials (14 August 2008), WHO International Clinical Trials Registry Platform (6 October 2009) and the National Research Register (NRR) Archive (to September 2007) to identify ongoing trials.

### Searching other resources

We handsearched Nutrition Abstracts and Reviews (publication database) from 1960 to 1983; Clinical Nutrition: Clinical nutrition: official journal of the European Society of Parenteral and Enteral Nutrition vol 1 to vol 27 (3) 2008; American Journal of Clinical Nutrition vol 2 to vol 88 (2) 2008; Journal of Parenteral and Enteral Nutrition vol 1 to vol 32 (2) 2008; and Proceedings of the Nutrition Society vol 1 to vol 67(3) 2008. We also checked reference lists of articles, searched books related to orthopaedics, geriatric medicine and nutrition, and corresponded with colleagues and investigators.

## Data collection and analysis

### Selection of studies

Both authors independently assessed reports of potentially eligible studies. All differences were resolved by discussion.

### Data extraction and management

We independently extracted data using a pre-derived data extraction form and entered the agreed results into Review Manager. All differences were resolved through discussion. If necessary, we contacted trialists for further information on methodology and data.

### Assessment of risk of bias in included studies

We continue to independently assess methodological quality using a subject-specific modification of the former generic evaluation tool developed by the Cochrane Bone, Muscle and Joint Trauma Group. Our tool assesses aspects of internal and external validity and scores each item between 0 and 2 (*see* Table 1). Additionally we separately rated the risk of bias from pre-allocation disclosure of assignment for presentation in the 'Risk of bias' table, an extension of the 'Characteristics of included studies'.

**Table 1. Methodological quality assessment items**

| Items and scores |
|---|
| a. Was the assigned treatment adequately concealed prior to allocation?<br>2 = method did not allow disclosure of assignment (A)<br>1 = small but possible chance of disclosure of assignment or states random but no description(B)<br>0 = quasi-randomised (C) |
| b. Were the outcomes of participants who withdrew described and included in the analysis (intention to treat)?<br>2 = intention-to-treat analysis based on all cases randomised possible or carried out<br>1 = states number and reasons for withdrawal but intention-to-treat analysis not possible<br>0 = not mentioned or not possible |

**Table 1. Methodological quality assessment items** (*Continued*)

| |
|---|
| c. Were the outcome assessors blinded to treatment status?<br>2 = action taken to blind assessors, or outcomes such that bias is unlikely<br>1 = small or moderate chance of unblinding of assessors<br>0 = not mentioned |
| d. Were the treatment and control group comparable at entry?<br>2 = good comparability of groups<br>1 = confounding small<br>0 = large potential for confounding, or not discussed |
| e. Were care programmes, other than the trial options, identical?<br>2 = care programmes clearly identical<br>1 = clear but unimportant differences<br>0 = not mentioned or clear and important differences in care programmes |
| f. Were the inclusion and exclusion criteria clearly defined?<br>2 = clearly defined<br>1 = inadequately defined<br>0 = not defined |
| g. Were the interventions clearly defined (including estimates of nutritional value)?<br>2 = clearly defined interventions are applied with a standardised protocol<br>1 = clearly defined interventions are applied but the application protocol is not standardised<br>0 = intervention and/or application protocol are poorly or not defined |
| h. Were the participants blind to assignment status following allocation?<br>2 = effective action taken to blind participants<br>1 = small or moderate chance of unblinding participants<br>0 = not possible, or not mentioned (unless double-blind), or possible but not done |
| i. Were the treatment providers blind to assignment status?<br>2 = effective action taken to blind treatment providers<br>1 = small or moderate chance of unblinding of treatment providers<br>0 = not possible, or not mentioned (unless double-blind), or possible but not done |
| j. Was follow-up active and appropriate?<br>2 = optimal<br>1 = adequate<br>0 = not defined or not adequate |
| k. Was the overall duration of surveillance clinically appropriate?<br>2 = optimal (six months or more)<br>1 = adequate (one up to six months)<br>0 = not defined, or not adequate |

### Measures of treatment effect

For each study, risk ratios and 99% confidence intervals were calculated for dichotomous outcomes and mean differences and 99% confidence intervals for continuous outcomes. The choice of 99% confidence intervals reflects the extra burden of proof we considered appropriate for individual trials, in view of their generally poor quality. Summary estimates for meta-analysis are provided as 95% confidence intervals.

### Unit of analysis issues

Although we would have included cluster randomised trials, the unit of randomisation in all of the included trials was the individual patient.

### Dealing with missing data

Mortality results have been presented using denominators based on the numbers of participants at randomisation (intention-to-treat analysis). Generally, the results for other outcomes have been presented using denominators based on the numbers of participants available at follow-up. In some cases, we investigated the effect of drop outs and exclusions by conducting worst scenario analyses for the primary outcomes, where those who were missing to follow-up in the intervention group were assumed to have the poorer outcome but not those who were missing in the control group. We were alert to the potential mislabelling or non identification of standard errors and standard deviations. Unless missing standard deviations could be derived from confidence intervals or standard errors, we did not assume values in order to present these in the analyses.

### Assessment of heterogeneity

Heterogeneity was assessed by visual inspection of the forest plot (analysis) along with consideration of the chi² test for heterogeneity and the $I^2$ statistic (Higgins 2003).

### Assessment of reporting biases

We considered there were insufficient data available to meaningfully assess publication bias by preparing a funnel plot. However, our search of 'grey literature', dogged pursuit of trials listed in clinical trial registers and contact with trial authors should have helped to avoid publication bias.

### Data synthesis

Where appropriate, the results of comparable groups of trials were combined using both fixed-effect and random-effects models, and results presented with 95% confidence intervals.

### Subgroup analysis and investigation of heterogeneity

Only subgroup analysis based on pre-existing nutritional status was performed. To test whether the subgroups were statistically significantly different from one another, we tested the interaction using the technique outlined by Altman 2003.

### Sensitivity analysis

We planned sensitivity analyses based on aspects of trial methodology. So far, we have explored the risk of bias associated with inadequate concealment of allocation. To test whether the subgroups were statistically significantly different from one another, we tested the interaction using the technique outlined by Altman 2003.

## RESULTS

### Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

### Results of the search

Overall, of the 66 studies identified via the search strategy: 24 are included, 36 are excluded, four are ongoing and two are awaiting assessment.

Only 13 included trials were identified via the MEDLINE search strategy. One further trial (Stableforth 1986), located via EMBASE, was indexed by MEDLINE, but was not retrieved by the first two phases of the optimum Cochrane search strategy for randomised controlled trials (Dickersin 1994; Higgins 2006). BIOSIS yielded two further studies (Bean 1994; Brown 1992). Gallagher 1992 was initially found from handsearching the Journal of Parenteral and Enteral Nutrition, but also appeared in the reference list of another published trial. Bean 1994 and Gallagher 1992 were only available as abstracts from conference proceedings. The two presently unpublished trials (Hankins 1996; Madigan 1994) and two previously unpublished trials (Duncan 2006; Espaulella 2000) were provided by personal contacts (Ian Cameron, Heidi Guyer, Donna Duncan and Antony Johansen). Bruce 2003, Houwing 2003 and Tidermark 2004 were initially identified by handsearching Clinical Nutrition and Neumann 2004 by searching Nutrition. A separate examination of the search strategy and findings prior to 2001 is available (Avenell 2001a). All 24 included trials were published in English.

### Included studies

Details of study methods, population, interventions and outcomes of individual trials are provided in the Characteristics of included studies.

Further details (including clarifications) on methodology, trial participants and outcome, sought from all studies, were obtained from trialists of 16 studies (Bastow 1983; Botella-Carretero 2008; Brown 1992; Bruce 2003; Day 1988; Duncan 2006; Eneroth 2006; Espaulella 2000; Hankins 1996; Hartgrink 1998; Houwing 2003; Miller 2006; Neumann 2004; Sullivan 1998; Sullivan 2004;

Tidermark 2004) and other sources for two trials (Ronald Koretz for Gallagher 1992; Jane Robertson for Hoikka 1980).

### Design

Twenty trials were randomised controlled trials, although seven of these gave no details of the method of randomisation. The other four trials (Bastow 1983; Brown 1992; Bruce 2003; Hoikka 1980) were quasi-randomised trials. There were no cluster or cross-over randomised trials.

### Sample sizes

The 24 included studies involved a total of 1940 participants. Sample size ranged from 10 participants in Brown 1992 to 318 participants in Duncan 2006.

### Setting

The publication dates of the trials span 28 years, Hoikka 1980 being the earliest. Most of the trials were based in a single centre. Trials were conducted in eight countries (Australia, Finland, the Netherlands, Spain, Sweden, Switzerland, UK, USA), with six trials being conducted in the UK, four each in Australia and the USA, and three in Switzerland.

### Participants

The majority of participants were female, and in seven studies (Bastow 1983; Bean 1994; Brown 1992; Bruce 2003; Duncan 2006; Stableforth 1986; Tidermark 2004) all participants were female. Sullivan 1998 and Sullivan 2004 were the only studies where male participants formed the majority. Where reported, the mean age of participants was usually over 80 years. Gallagher 1992 gave no details on age, but the rest of the details provided in the abstract were compatible with an older population. Only Bean 1994 applied an upper age limit, this being 85 years.

All studies (except Miller 2006 which included participants with lower limb fractures) included only participants with hip fracture. Separate data for participants with hip fracture have been obtained for Miller 2006. Eleven studies (Day 1988; Delmi 1990; Eneroth 2006; Espaulella 2000; Hartgrink 1998; Schürch 1998; Stableforth 1986; Sullivan 1998; Sullivan 2004; Tidermark 2004; Tkatch 1992) provided information on the types of hip fractures suffered by the participants. Nine studies (Bastow 1983; Bean 1994; Brown 1992; Delmi 1990; Eneroth 2006; Espaulella 2000; Schürch 1998; Tidermark 2004; Tkatch 1992) excluded people with dementia or severe cognitive dysfunction. Many of the studies excluded people with a wide range of medical conditions. Seven studies (Day 1988; Duncan 2006; Espaulella 2000; Hankins 1996; Houwing 2003; Sullivan 1998; Sullivan 2004) indicated that consent (assent) was acceptable if given by a relative or guardian.

Six studies, involving 363 participants, examined the effect of supplementation on malnourished participants (Bastow 1983; Bean 1994; Brown 1992; Gallagher 1992; Hankins 1996; Miller 2006). Only Gallagher 1992 defined participants as malnourished on the basis of serum albumin; the remaining studies used anthropometric measurements, such as mid-upper arm circumference.

### Interventions

The 24 included trials evaluated a variety of nutritional supplements, mostly in comparison with a control group. Details of these and the method of delivery in individual studies are provided in the Characteristics of included studies. The comparisons under test fell into five categories (as detailed below).

Madigan 1994 had three groups: the two supplemented groups (one with a multivitamin and mineral supplement) were subsequently combined in the report, owing to small numbers at follow-up. Since these two groups both fit the criterion in this review for a "multinutrient" supplement group, the combined results for these two groups, compared to the control, are also presented here. Botella-Carretero 2008 also had three groups: oral protein and energy, oral protein, and control; both supplemented groups have been combined for this report, also owing to small numbers. Miller 2006 had four groups: a nutrition supplementation group, a physical activity intervention group, a combined intervention group, and an attention control group. Only data from the nutrition supplementation only and control groups are used here.

The following comparisons were made:

#### Multinutrient supplements (oral, nasogastric, intravenous) versus control

The multinutrient supplements under test usually provided non-protein energy, protein, some vitamins and minerals. These were delivered either orally, via a nasogastric tube, intravenously, or combinations of these.

##### *Oral supplements*

Ten studies (Botella-Carretero 2008; Brown 1992; Bruce 2003; Delmi 1990; Hankins 1996; Houwing 2003; Madigan 1994; Miller 2006; Stableforth 1986; Tidermark 2004) involved 538 participants.

##### *Nasogastric tube feeding*

Four studies (Bastow 1983; Gallagher 1992; Hartgrink 1998; Sullivan 1998) involved 377 participants.

##### *Nasogastric tube feeding and oral supplements*

One study (Sullivan 2004) involved 57 participants.

##### *Intravenous feeding and oral supplements*

One study (Eneroth 2006) involved 80 participants.

**High protein containing supplements versus low-protein or non-protein containing supplements**

Protein supplementation was delivered within oral feeds.
Four studies (Espaulella 2000; Neumann 2004; Schürch 1998; Tkatch 1992) involving 371 participants. Whereas the protein supplement resulted in extra calories in the intervention group in Tkatch 1992, the energy content of both intervention and placebo groups were equivalent in Espaulella 2000 and Schürch 1998. Moderate quantities of minerals and vitamins were also provided with the protein supplement in Espaulella 2000 and Schürch 1998; none were in sufficient doses to detract from these being predominantly protein supplements. In Neumann 2004 there were differences in vitamin and mineral intakes between the high- and lower-protein supplements, and the carbohydrate intake in the lower-protein supplement resulting in similar energy contents of the two supplements.

**Vitamin supplement versus control**

Two studies (Day 1988; Hoikka 1980) involved 97 participants. Day 1988 investigated the intravenous thiamin (vitamin B1) and water soluble vitamins versus control. Hoikka 1980 investigated the use of oral vitamin D versus control.

**Isonitrogenous ornithine alpha-ketoglutarate versus peptide supplement**

Ornithine alpha-ketogluturate is metabolised in part to the amino acid glutamine, and is used to improve nitrogen conservation. The interventions were probably delivered orally. One study (Bean 1994) involved 59 participants.

**Dietetic assistants versus usual care**

Provision of extra assistance in the form of dietetic assistants, above that of dietitians and nurses, to help improve people's dietary intake. One study (Duncan 2006) involved 318 participants.

## Excluded studies

The reasons for excluding 36 studies are given in the Characteristics of excluded studies. Six excluded studies were published in languages other than English, sufficient translation having been obtained to establish non-eligibility.

### Ongoing studies

Details of four ongoing trials are given in the Characteristics of ongoing studies.

### Studies awaiting classification

Details of the two studies in this category are given in the Characteristics of studies awaiting classification. Requests for further details have been sent to the trial investigators.

### New studies found this update

Of the 10 newly identified studies for this update, one new trial is included (Botella-Carretero 2008), five trials are excluded ( Boudville 2002; Hommel 2007; Thomas 2008 ; Kacmaz 2007; Oloffson 2007), one awaits classification, pending further information from the trial investigators (Gerstorfer 2008), and three trials are ongoing (Dagnelie; Houdijk; Miller). One former ongoing trial is now included (Eneroth 2006); as is one trial formerly awaiting classification (Miller 2006).

## Risk of bias in included studies

The quality of trial methodology, as reported, was disappointing and risk of bias associated with poor trial methods could not be ruled out. Many of the trials failed to report trial methodology in sufficient detail to give top scores on individual items (*see* Table 1 for scoring scheme and Table 2 for results). The impression that the scores for these studies more reflect the quality of reporting rather than trial methodology was strengthened by the changed, generally increased, scores of some items of eight studies upon gaining additional information from the trialists (Brown 1992; Bruce 2003; Day 1988; Espaulella 2000; Hankins 1996; Hartgrink 1998; Houwing 2003; Sullivan 1998).

**Table 2. Methodological quality assessment: results for individual trials**

| Comparison | Items (defined in Table 1) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study ID** | **a** | **b** | **c** | **d** | **e** | **f** | **g** | **h** | **i** | **j** | **k** |
| **1. Multinutrient supplement (oral, nasogastric, intravenous)versus control**<br>**a. Oral supplements** | | | | | | | | | | | |
| Botella-retero 2008 | 2 | 1 | 0 | 2 | 0 | 2 | 2 | 0 | 0 | 2 | 1 |

**Table 2. Methodological quality assessment: results for individual trials** (*Continued*)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Brown 1992 | 0 | 2 | 2 | 1 | 0 | 2 | 0 | 0 | 0 | 1 | 0 |
| Bruce 2003 | 0 | 1 | 0 | 2 | 1 | 2 | 2 | 0 | 0 | 1 | 2 |
| Delmi 1990 | 1 | 1 | 0 | 2 | 0 | 2 | 2 | 0 | 0 | 2 | 2 |
| Hankins 1996 | 2 | 2 | 0 | 2 | 1 | 2 | 2 | 0 | 0 | 2 | 1 |
| Houwing 2003 | 2 | 2 | 1 | 2 | 0 | 2 | 1 | 1 | 1 | 1 | 0 |
| Madigan 1994 | 1 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 2 | 1 |
| Miller 2006 | 2 | 2 | 2 | 1 | 0 | 2 | 2 | 0 | 0 | 1 | 1 |
| Stableforth 1986 | 1 | 1 | 0 | 0 | 2 | 2 | 1 | 0 | 0 | 2 | 0 |
| Tidermark 2004 | 1 | 2 | 0 | 1 | 2 | 2 | 0 | 0 | 0 | 2 | 2 |
| **b. Nasogastric tube feeding** | | | | | | | | | | | |
| Bastow 1983 | 0 | 2 | 0 | 1 | 1 | 2 | 1 | 0 | 0 | 1 | 0 |
| Gallagher 1992 | 1 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 0 |
| Hartgrink 1998 | 1 | 1 | 0 | 2 | 2 | 2 | 2 | 0 | 0 | 2 | 0 |
| Sullivan 1998 | 2 | 2 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 2 | 2 |
| **c. Nasogastric tube feeding and oral supplements** | | | | | | | | | | | |

**Table 2. Methodological quality assessment: results for individual trials** (*Continued*)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sullivan 2004 | 2 | 2 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 2 | 2 |
| **d. Intravenous feeding and oral supplements** | | | | | | | | | | | |
| Eneroth 2006 | 1 | 2 | 0 | 1 | 2 | 2 | 2 | 0 | 0 | 2 | 1 |
| **2. High protein containing supplement versus low protein or non-protein containing supplement** | | | | | | | | | | | |
| Espaulella 2000 | 2 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Schürch 1998 | 1 | 1 | 0 | 2 | 0 | 2 | 2 | 2 | 1 | 2 | 2 |
| Tkatch 1992 | 1 | 0 | 0 | 1 | 0 | 2 | 2 | 1 | 0 | 2 | 2 |
| Neumann 2004 | 1 | 1 | 0 | 2 | 0 | 2 | 2 | 1 | 1 | 1 | 1 |
| **3. Vitamin supplement versus control**<br>**a. Thiamin (vitamin B1) and water soluble vitamins** | | | | | | | | | | | |
| Day 1988 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 0 | 0 | 2 | 1 |
| **b. Vitamin D** | | | | | | | | | | | |
| Hoikka 1980 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 1 | 1 | 1 | 2 |
| **4. Isonitrogenous ornithine alpha-ketoglutarate versus peptide supplement** | | | | | | | | | | | |
| Bean 1994 | 1 | 2 | 0 | 0 | 0 | 2 | 1 | 2 | 2 | 2 | 2 |
| **5. Dietetic assistants versus usual care** | | | | | | | | | | | |
| Duncan 2006 | 2 | 1 | 2 | 2 | 1 | 1 | 2 | 0 | 0 | 1 | 1 |

### Allocation concealment

Concealment of allocation (item a) was confirmed in seven trials ( Botella-Carretero 2008; Duncan 2006; Espaulella 2000; Hankins 1996; Miller 2006; Sullivan 1998; Sullivan 2004) that used sealed, opaque envelopes and in Houwing 2003, which used computer generated allocation applied independently of the main trial investigator. Though numbered sealed and opaque envelopes were used in Tidermark 2004, the preparation and opening of these was by the same person. Similarly, there was no report of safeguards in Eneroth 2006, where closed envelopes were administered by a research nurse. Allocation was unlikely to be concealed in the four quasi-randomised studies (Bastow 1983; Brown 1992; Bruce 2003; Hoikka 1980). Of the remaining 10 trials, three gave incomplete details and seven gave no details at all of the randomisation process.

### Intention-to-treat analysis

Although not usually explicitly stated in the methods sections, intention-to-treat analysis (item b) was carried out in 11 studies (Bastow 1983; Bean 1994; Brown 1992; Day 1988; Eneroth 2006; Hankins 1996; Houwing 2003; Miller 2006; Sullivan 1998; Sullivan 2004; Tidermark 2004). In four studies, participants were excluded after randomisation because of poor compliance with dietary supplementation (Espaulella 2000; Hankins 1996; Madigan 1994; Tkatch 1992); data on some of these participants were later obtained from Hankins 1996 and Espaulella 2000.

### *Blinding*

Of the eight studies where blinding of participants (item h) and treatment providers (item i) was theoretically practical (Bean 1994; Day 1988; Espaulella 2000; Hoikka 1980; Houwing 2003; Neumann 2004; Schürch 1998; Tkatch 1992), only two (Bean 1994; Espaulella 2000) confirmed that participants and treatment providers were blinded to the intervention. Hoikka 1980 claimed to be double-blind but failed to clarify to whom this applied. Differences in the look and taste of active and placebo supplements in Houwing 2003 may have prevented effective blinding of outcome assessment. Neumann 2004 claimed to be double-blind but provided no details on how this was achieved. Whilst blinded outcome assessment (item c) is difficult for some interventions such as those involving the use of a nasogastric tube, it should be possible for other interventions, and becomes easier after the intervention has ended. This was the case in point for Duncan 2006, where there was blinded assessment of the trial participant's progress through rehabilitation.

### Baseline comparability

Although 17 trials had comparability of the groups at baseline (item d) or only a small chance of confounding, details of the nutritional status of the groups were often missing. Related to this is the lack of information on anthropometric parameters. While it is difficult to measure height and weight in people with hip fracture, seven trials failed to provide information about any baseline anthropometry; for example, mid-upper arm circumference, or weight. An appraisal of the trials for baseline imbalances in the nutritional risk revealed only a reported imbalance in weight, where participants receiving supplementation were on average heavier, in Stableforth 1986. However, body mass index, which is a more relevant measure of nutritional status than weight, was not available for this trial.

### Care programme comparability

Only six trials (Day 1988; Eneroth 2006; Espaulella 2000; Hartgrink 1998; Stableforth 1986; Tidermark 2004) reported or provided confirmatory evidence that care programmes (item e) were the same in both intervention and control groups.

### External validity and outcome assessment

Inclusion and exclusion criteria (item f) were well defined in these trials.

Fifteen studies (Botella-Carretero 2008; Bruce 2003; Day 1988; Delmi 1990; Eneroth 2006; Espaulella 2000; Hankins 1996; Hartgrink 1998; Hoikka 1980; Madigan 1994; Miller 2006; Neumann 2004; Schürch 1998; Sullivan 1998; Tkatch 1992) gave clear details of the exact nutritional content of the nutrients administered and of the protocol for application of the supplement (item g).

Follow-up of trial participants was generally active and appropriate (item j) in terms of outcome assessment.

Recovery from hip fracture in older people takes time, with long term implications for morbidity and functional status. The duration of surveillance (item k) was not clearly defined in four studies (Bastow 1983; Botella-Carretero 2008; Brown 1992; Gallagher 1992) and was generally too short, with seven studies following participants up for less than three months. Eleven studies followed up participants for six months or over; Schürch 1998 and Miller 2006 followed up participants for one year.

## Effects of interventions

The outcomes reported in the included studies are listed in the Characteristics of included studies. These are grouped by 'main' (primary and secondary) outcomes and 'other' outcomes, as defined in the Types of outcome measures. The results presented here concentrate on main outcomes.

The included studies often failed to report main outcomes. For example, only one trial (Tidermark 2004) reported participants' perceived quality of life after discharge and on fracture healing. Though in the 'other' outcomes category, it was notable that carer burden and stress, and economic outcomes were also not reported. Postoperative complications were reported as a wide variety of individual conditions (including diarrhoea, nausea, vomiting, aspiration pneumonia, gastrointestinal ulcer, pressure sore, face flushing, deep hip joint infection, chest infection, urinary tract in-

fection, deep venous thrombosis, pulmonary embolism, thrombophlebitis, ischaemic heart disease, cardiac failure, anaemia, hyponatraemia, confusion, anaphylaxis, and acute renal failure) and generic complications (gastrointestinal, surgical, infection, postoperative, life-threatening). Those presented for individual studies are noted in the Characteristics of included studies. In order to give a more complete picture of morbidity, we opted to present the number of participants with complications at the end of individual studies. Results were not used from those studies, such as Tkatch 1992, which provided the numbers of complications but not the numbers of participants with complications. Results from Houwing 2003 were also not pooled since this trial only recorded pressure sores.

Where possible, the numbers of trial participants with 'unfavourable outcome' have been presented. As defined above, this is the sum of the participants who had died plus the survivors with complications. For most studies, this result could not be deduced from the available data. Results for 'unfavourable outcome' based on a slightly different definition (mortality or survivors with a major complication or two or more minor complications) originally presented in Delmi 1990, were available for three studies (Delmi 1990; Hankins 1996; Tkatch 1992) and are used in this review.

Mortality results have been presented using denominators based on the numbers of participants at randomisation (intention-to-treat analysis). Generally, the results for other outcomes have been presented using denominators based on the numbers of participants available at follow-up. Exceptions to this are noted below.

Lengths of hospital stay in the acute hospital and rehabilitation hospital were often reported but have not been presented in the analyses, or pooled. This is because, even when means and standard deviations (SD) for these outcomes have been reported, it is unlikely that lengths of stay were normally distributed.

In the following, results are presented for the fixed-effect model. Where the conclusions reached by combining comparable groups of trials differed noticeably between the fixed-effect and random-effects models, the results for the random-effects models are also presented.

### Multinutrient supplements (oral or nasogastric routes, or both) versus control

Below we present the separate results by the route (oral, nasogastric or both) used for multinutrient supplementation, and then discuss the overall results for multinutrient supplementation. Finally, we investigate whether the results varied, according to whether the trials specifically targeted people who were malnourished, or according to trial quality (represented by the whether allocation was concealed or not).

#### Oral supplements

Ten studies evaluated the effect of oral multinutrient supplementation (Botella-Carretero 2008; Brown 1992; Bruce 2003; Delmi 1990; Hankins 1996; Houwing 2003; Madigan 1994; Miller 2006; Stableforth 1986; Tidermark 2004) of which three (Brown 1992; Hankins 1996; Miller 2006) targeted people who were malnourished. Pooling of the mortality data from nine studies ( Houwing 2003 did not provide mortality data) showed no statistically significant difference between the two groups in mortality (*see* Analysis 1.1: risk ratio (RR) 0.76, 95% confidence interval (CI) 0.42 to 1.37). Bruce 2003 reported similar percentages of participants in the two groups who had died or were in a nursing home at six months (23.4% versus 24.6%).

Six studies (Botella-Carretero 2008; Delmi 1990; Hankins 1996; Madigan 1994; Stableforth 1986; Tidermark 2004) reported the numbers of participants with complications at the end of the study. Results from Houwing 2003 were not included since these were only for pressure sores: there was no statistically significant difference between the two groups in the numbers of participants with this complication. Pooled results from six studies showed a reduction, which was not statistically significant, in the participants with complications in the supplemented group (*see* Analysis 1.2: RR 0.81, 95% CI 0.58 to 1.13).

Although data pooled using the fixed-effect model from four trials for the combined outcome for mortality or complications ('unfavourable outcome') at final follow-up tended to favour the supplemented group (*see* Analysis 1.4: RR 0.76, 95% CI 0.55 to 1.04), there was significant heterogeneity ($Chi^2 = 4.84$, df = 2 (P = 0.09); $I^2 = 59\%$). The pooled results using the random-effects model showed no statistically significant difference (*see* Analysis 1.5: RR 0.71, 95% CI 0.41 to 1.22). Delmi 1990 presented results, without explanation of the missing participants, for only 52 participants out of the 59 originally randomised. Exploratory analyses based on numbers randomised (in all trials where available) in which it was assumed that all excluded participants in the supplemented group had complications at follow-up, for 'unfavourable outcome' (*see* Analysis 1.6: RR 0.85, 95% CI 0.62 to 1.15) again showed no statistically significant difference between the two groups.

Hankins 1996 also presented data for 'unfavourable outcome' in the acute hospital (*see* Analysis 1.6: RR 0.96, 99% CI 0.64 to 1.44) and post discharge (*see* Analysis 1.6: RR 1.10, 99% CI 0.39 to 3.09). Delmi 1990 presented data for similar outcomes but gave insufficient explanation of the denominators used in their report.

The duration of hospital stay was reported in eight studies. The data for those trials that allowed significance testing are presented in Table 3. Botella-Carretero 2008 reported that hospital stay was similar for all three groups (the graph of these data clearly showed no statistically significant differences). Brown 1992 reported a lower acute hospital stay for the supplementation group (27 days versus 48 days: mean difference -21.00 days, 99% CI -65.15 to 23.15 days). Bruce 2003 reported no significant difference between the two groups in the mean length of hospital stay (17.7 days versus 16.6 days: mean difference 1.10 days, 99% CI -3.53 to 5.73 days). Delmi 1990 reported a statistically significantly lower median length of stay in acute and rehabilitation wards for the

supplementation group (24 days (range 13 to 157) versus 40 days (range 10 to 259); reported P < 0.02). Hankins 1996 found that supplemented participants had a median acute and rehabilitation stay of 26 days (range 6 to 60) versus 21 days (range 3 to 60) for participants in the control group (reported P = not significant). Madigan 1994 found that the acute hospital stay was 16 days in the combined intervention group and 15 days in the control group (mean difference 1.00 day, 99% CI -8.51 to 10.51 days). Both groups, including several patients with other lower-limb fractures, in Miller 2006 stayed a median of 24 days for in hospital. Tidermark 2004 reported no significant difference in median hospital stay during the first year after surgery in intervention and control groups (20 days (range 5 to 356 days) versus 27 days (range 5 to 197 days)).

**Table 3. Length of hospital stay data used for significance testing**

| Study ID | Intervention (n, mean, sd) | | | Control (n, mean, sd) | | | Mean difference (99% confidence interval) |
|---|---|---|---|---|---|---|---|
| **Oral supplements** | | | | | | | |
| Brown 1992 | 5 | 27.00 | 10.00 | 5 | 48.00 | 37.00 | -21.00 days (-65.15 to 23.15) |
| Bruce 2003 | 50 | 17.70 | 9.40 | 58 | 16.60 | 9.20 | 1.10 days (-3.53 to 5.73) |
| Madigan 1994 | 18 | 16.00 | 8.00 | 12 | 15.00 | 11.00 | 1.00 day (-8.51 to 10.51) |
| **Nasogastric tube feeding** | | | | | | | |
| Sullivan 1998 | 8 | 38.20 | 36.90 | 7 | 23.70 | 20.00 | 14.50 days (-24.34 to 53.34) |
| **High protein supplements** | | | | | | | |
| Espaulella 2000 | 85 | 16.40 | 6.60 | 86 | 17.20 | 7.70 | -0.80 days (-3.62 to 2.02) |
| Neumann 2004 | 18 | 23.20 | 5.52 | 20 | 28.00 | 11.63 | -4.80 days (-12.29 to 2.69) |
| **Vitamin B1** | | | | | | | |
| Day 1988 | 28 | 35.00 | 34.00 | 30 | 29.00 | 30.00 | 6.00 days (-15.75 to 27.75) |

sd: standard deviation

Bruce 2003 reported no significant differences between the two groups in functional outcomes (fall in the Katz activities of daily living score: 41.7% versus 33.9%) or living at home at six months (63.8% versus 63.2%). Hankins 1996 found no statistically significant effect of the supplement at two months on the Barthel Index of functional ability; median 56 (range 0 to 100) versus 40 (range 0 to 92). Madigan 1994 found that the combined intervention group were more likely to return to their premorbid mobility (non-return: 9/18 versus 7/12; RR 0.86, 99% CI 0.36 to 2.05; analysis not shown), but this may have related to the fact that significantly more supplemented participants were sent to a rehabilitation hospital. Activities of daily living, assessed by the Katz score, in Tidermark 2004, were better maintained in the supplemented group at six months (dependence in bathing and one other function: 2/18 versus 8/16; RR 0.22, 99% CI 0.04 to 1.39; analysis not shown) but less so at 12 months (4/18 versus 6/16; RR 0.63, 99% CI 0.15 to 2.59; analysis not shown), compared with the control group. Tidermark 2004 also found that mobility data were not significantly different between the two groups.

Tidermark 2004 reported no significant difference between the two groups for health related quality of life at six and 12 months, as assessed by the EuroQol questionnaire.

Tidermark 2004 found no significant difference between the two groups in fracture healing complications (4/18 versus 7/17; RR 0.54, 99% CI 0.14 to 2.10; analysis not shown).

Botella-Carretero 2008 reported mean consumption of 41% for the protein supplement and 51% for the protein and energy supplement. Bruce 2003 reported a mean consumption of 20.6 cans of supplement, out of a maximum possible of 28. Delmi 1990 reported that the supplement did not reduce volitional food intake, and compliance appeared not to be a problem. Hankins 1996 found that only 65% of participants managed to complete the full 30 days of supplementation, however, the supplement had no significant effect on ordinary food intake. Houwing 2003 found that the mean daily intake of the active or placebo supplements was 77% in both groups. Madigan 1994 also found that the oral supplement did not significantly affect volitional intake, but made no comment on compliance. Neither Brown 1992, Tidermark 2004 nor Stableforth 1986 gave details on volitional food intake or compliance with the supplements. Specific data on adherence for participants with hip fracture in the nutrition-supplementation only group of Miller 2006 were not available.

#### Nasogastric tube feeding

Four studies examined nasogastric multinutrient supplementation (Bastow 1983; Gallagher 1992; Hartgrink 1998; Sullivan 1998). Gallagher 1992, which was only published as an abstract, gave no denominators and so could not be included in the meta-analyses. Information provided by Ronald Koretz (personal communication), based on notes taken at a conference presentation by Gallagher 1992, indicated a possible failure to undertake intention-to-treat analysis. It seems likely that 12 participants allocated to the intervention group, who had feeding discontinued when their tube was pulled out, were crossed over to the control group in the analysis. There were also some differences in the results presented at the conference and in the published abstract.

Gallagher 1992 gave no information on deaths in the published abstract; two deaths were reported in the conference presentation. Pooling of mortality data from the other three studies showed no evidence of an effect (*see* Analysis 1.1: RR 0.99, 95% CI 0.50 to 1.97). However considerable heterogeneity for mortality exists between the studies ($chi^2 = 6.44$, P = 0.04; $I^2 = 68.9\%$). All seven deaths in Hartgrink 1998 occurred in the intervention group during the two-week period of observation. This could have been due to chance, as the deaths were not obviously related to tube feeding (anaesthetic death, cardiac arrest, stroke and multi-organ failure), and did not appear to relate to aspiration pneumonia, a complication of tube feeding. Four of the deaths occurred in participants in whom tube feeding had not started, although the tube had been placed. It was evident that tube feeding was poorly tolerated, with only 26% of the intervention group tolerating feeding for the full two weeks. Conversely all five deaths occurred in the control group in Sullivan 1998; this might in part reflect the greater frailty of the control group at recruitment.

The four trials were heterogeneous in the nutritional status of the study participants. Unlike Hartgrink 1998, Bastow 1983 targeted nasogastric feeding on thin and very thin participants, defined by anthropometry. Seventy-eight per cent of participants tolerated nasogastric feeding until discharge from the ward, although 18 in the intervention group developed diarrhoea, which was ascribed to antibiotics in 16. Bastow 1983 did not report gastrointestinal complications in the control group. Hospital mortality was reduced in the very thin group (2/25 versus 5/25; RR 0.37, 99% CI 0.05 to 2.78) rather than in the thin group (5/39 versus 4/35; RR 1.12, 99% CI 0.22 to 5.67); analyses not shown (test for interaction based on 95% CI: P = 0.27). Malnourished participants were not specifically targeted in Sullivan 1998. In Sullivan 1998, the intervention group received supplements until discharge or until a good oral intake was achieved. Patients with low serum albumin readings, described as malnourished, were targeted in Gallagher 1992.

Only Sullivan 1998 provided data on participants developing medical complications in intervention and control groups (*see* Analysis 1.2: RR 1.09, 99% CI 0.64 to 1.86), and no study provided information on 'unfavourable outcome'. Sullivan 1998 reported that three out of eight in the intervention group had bloating in the early morning and none in the control group; there was no feed-induced diarrhoea. Sullivan 1998 did not report on aspiration pneumonia.

Three studies provided information on length of hospital stay. In the published abstract, Gallagher 1992 found that rehabilitation

length of stay was 25 days in the intervention group and 33 days in the control group (reported P = 0.058). However, in the notes taken from the conference presentation by Gallagher 1992, the length of stay was 22.7 days for the control group and 22.6 days for the intervention group. Sullivan 1998 reported no significant difference between the two groups in the length of acute care stay for survivors (38.2 days versus 23.7 days: mean difference 14.50 days, 99% CI -24.34 to 53.34 days). Bastow 1983 stated the median length of stay for the very thin group only (including those who died): a median of 29 days for the intervention group and 38 days for the control group (reported P = 0.04). Hartgrink 1998 gave no information about length of stay but reported that the intervention group were less likely to have left hospital by two weeks (still in hospital at two weeks: 55/62 versus 53/67; RR 1.12, 99% CI 0.92 to 1.37; analysis not shown).

Where reported, physiotherapy goals were achieved more quickly in the intervention groups: Gallagher 1992 (published abstract), 12.7 days versus 16.2 days (reported P = not significant); Bastow 1983 thin group: 10 days (range 4 to 20) versus 12 days (range 5 to 26) (reported P = 0.04); Bastow 1983 very thin group: 16 days (range 5 to 34) versus 23 days (range 10 to 45) (reported P = 0.02). Sullivan 1998 showed no statistically significant difference between intervention and control groups for activities of daily living at discharge (Katz index (0 = independent to 12 = totally dependent): 4.1 versus 5.9; mean difference -1.80, 99% CI -7.17 to 3.57).

Sullivan 1998 found that volitional food intake was not significantly affected by nasogastric feeding. Bastow 1983 found that nasogastric feeding significantly suppressed oral intake in the thin group but not in the very thin group. The suppression of food intake in the thin group amounted to 1.1 MJ, compared with daily nasogastric feeding which provided 4.2 MJ.

#### Nasogastric tube feeding and oral supplements

Sullivan 2004 evaluated nightly nasogastric feeding tailored to the calculated energy requirements of individual participants after taking account of the intake from meals. If the difference between calculated requirements and food intake decreased to 240-480 kcal/day participants were asked to drink one or two cans of the supplement orally instead of nasogastric feeding. This regimen was compared with standard care. At six months there were no statistically significant differences between the two groups in mortality (*see* Analysis 1.1: RR 0.74, 99% CI 0.16 to 3.37) or post operative complications (*see* Analysis 1.2: RR 1.11, 99% CI 0.66 to 1.87).

There was no significant difference in hospital length of stay. The median (interquartile range) length of hospital stay for the intervention group was 9 days (7 to 21) and for the control group 9 days (7 to 15), reported P = 0.817).

Sullivan 2004 found no significant differences between intervention and control groups in the Katz Index of activities of daily living scores on discharge (median (interquartile range): 8 (4 to 11) versus 9 (7 to 11); reported P = 0.503), or the rate of discharge to an institution (25/27 versus 27/30; RR 1.03, 99% CI 0.83 to 1.27; analysis not shown).

Five of the 27 intervention group participants never started tube feeding because of either refusal of tube placement or lack of toleration of the feeding tube. Targeted tube feeding was continued until the oral intake was deemed to be adequate in only five of the remainder, and only two participants required no tube reinsertions. Though there was no significant difference between the two groups in the incidence of diarrhoea (5/27 versus 3/30; RR 1.85, 99% CI 0.32 to 10.68; analysis not shown), Sullivan 2004 reported that the diarrhoea in the intervention group was more difficult to control. In the first week, the intervention group met 86% of their calculated energy requirements compared with 63% for the control group (reported P = 0.002); the difference between the two groups was not significant for the 22 trial participants assessed in the second week (96% versus 95%; reported P = 0.942).

#### Intravenous feeding and oral supplements

Eneroth 2006 evaluated three days of intravenous feeding followed by seven days of oral supplements compared with standard care. Mortality was not significantly reduced (*see* Analysis 1.1: RR 0.11, 99% CI 0.00 to 4.95), but there was a significant reduction in participants with complications (*see* Analysis 1.2: RR 0.21, 99% CI 0.08 to 0.59). The mean length of hospital stay for both groups was 12.5 days. There was no significant difference between the two groups for those who were discharged to their own homes (14/40 versus 22/40, RR 0.64, 99% CI 0.33 to 1.24; analysis not shown).

#### Multinutrient supplements - overall results

Overall mortality from pooling the results of oral, nasogastric and intravenous multinutrient supplementation studies was similar in the intervention and control groups (*see* Analysis 1.1: RR 0.77, 95% CI 0.51 to 1.15).

The number of participants with complications was reduced in intervention compared with control groups when using the fixed-effect model (see Analysis 1.2: RR 0.71, 95% CI 0.57 to 0.89). However there was substantial heteogeneity for this outcome ($I^2$ = 70%, $chi^2$ = 23.63, P = 0.001). The result using the random-effects model was no longer statistically significant (see Analysis 1.3: RR 0.73, 95% CI 0.47 to 1.12). The significant heterogeneity was completely lost by removing Eneroth 2006 ($I^2$ = 0%, $chi^2$ = 5.63, P = 0.47) and yielded a non-effect (RR 0.99; 95% CI 0.32 to 10.68) from the pooled results of the remaining seven trials; analysis not shown.

There were no data from nasogastric groups or intravenous groups on 'unfavourable outcome' (*see* Analysis 1.4).

#### Subgroup and sensitivity analysis

### *Nutritional status of trial populations*

Subgrouping the trials according to whether they targeted malnourished participants showed a potential benefit in terms of mortality for supplementation in those which targeted malnourished participants (*see* Analysis 2.1: RR 0.52, 95% CI 0.25 to 1.07). Both visually and based on $I^2$ statistics, there was some indication of low to moderate heterogeneity ($I^2$ = 32%; $chi^2$ = 10.29, P = 0.17) in the subgroup of trials that did not target malnourished participants (RR 0.92, 95% CI 0.56 to 1.53). However, the results of the groups were not statistically significantly different from each other (test for interaction: two tailed z-test = 0.21) and thus there is no evidence to confirm that malnourished participants are more likely to benefit. The analyses for complications (*see* Analysis 2.2) and 'unfavourable outcome' (*see* Analysis 2.3) are also presented, but the greatly reduced available data for people who were malnourished limit their usefulness.

### *Methodological quality*

In previous versions of the review, we subgrouped the results for mortality according to the overall score for the methodological quality of individual trials. This gave inconclusive results but in recognition of the lack of evidence of a relationship between validity and summary scores *(*Juni 1999*)* we decided to test instead the effects of whether allocation was concealed or not. The results for mortality subgrouped by whether allocation was concealed (Risk of bias table: Yes) or may have been concealed but insufficient information was available (Unclear) or was not concealed as in the use of quasi-randomised methods (No) are presented in Analysis 3.1. A test for interaction confirms the visual impression that the pooled results of the four trials with confirmed allocation concealment are not statistically significantly different from those of the three trials where allocation was not concealed (test for interaction: two tail z-test = 0.23). However, a test of interaction shows the results of the trials with confirmed allocation concealment and those of trials where the status of concealment is unclear are statistically significantly different from each other (two tail z-test = 0.03). The 'unclear concealment' group is clearly heterogenous ($chi^2$ = 8.36, P = 0.08; $I^2$ = 52%) and we think it is inadvisable to draw any conclusions from the above test of interaction result.

## High protein containing supplements versus low-protein or non-protein containing supplements

Three studies (Espaulella 2000; Schürch 1998; Tkatch 1992) investigated whether approximately 20 g of protein provided within an oral supplement on a daily basis influenced outcome from hip fracture. Neumann 2004 investigated whether an high-protein supplement providing an extra 12.2 g or more of protein (with some differences in vitamins and minerals also) influenced outcome. All four studies failed to carry out intention-to-treat analyses (although information was later provided on mortality and hospital complications of excluded participants in Espaulella 2000). Denominators are sometimes missing or unclear. Tkatch 1992 excluded some of the intervention group for poor compliance with supplement taking, whilst some of the controls were excluded for later taking a dietary supplement. Espaulella 2000 excluded five people from the intervention group and three from the control group for protocol violations, and two from the control group because they were unable to swallow. Thus, unavoidably, the results presented here are not intention-to-treat analyses. No significant effect on mortality could be demonstrated (*see* Analysis 4.1: RR 1.42, 95% CI 0.85 to 2.37). An 'unfavourable outcome' (for Espaulella 2000: death or complication by the end of the study; for Tkatch 1992: death by the end of the study or, for survivors, a major complication or two or more minor complications present at the end of the study) was significantly reduced by protein supplementation (*see* Analysis 4.2: RR 0.78, 95% CI 0.65 to 0.95); this outcome was not reported by Schürch 1998. An exploratory analysis looking at the effect of assuming that all excluded participants in the protein supplementation group had an 'unfavourable outcome' could not be undertaken. However the results for Espaulella 2000 should be viewed in the context of the greater number of deaths in the protein supplementation group. In Tkatch 1992, neither the results for unfavourable outcome in acute hospital (9/33 versus 13/29; RR 0.61, 99% CI 0.25 to 1.50) nor in rehabilitation hospital (4/19 versus 14/22; RR 0.33, 99% CI 0.10 to 1.12) were statistically significant; analyses not shown. None of the four trials provided sufficient information to evaluate numbers of participants with complications at the end of the study. Espaulella 2000 reported that 44 out of 61 in the intervention group and 57 of 67 in the control group developed at least one complication during the six months of the study (RR 0.85, 99% CI 0.66 to 1.08; analysis not shown). Neumann 2004 reported that there were no differences between the groups for complications or adverse events.

Espaulella 2000 reported an acute hospital stay of 16.4 days in the intervention group and 17.2 days in the control group (mean difference -0.80 days, 99% CI -3.62 to 2.02 days). Tkatch 1992 reported a statistically significantly (P < 0.05) lower median length of acute and rehabilitation hospital stay in the intervention group (combined stay: median 69.4 days versus 101.6 days; acute hospital stay: median 23.5 days versus 24.7 days; rehabilitation hospital: 78.6 days versus 91.8 days). Schürch 1998 reported mean figures of 18.0 days versus 16.9 days on the acute ward, and median stays of 33 versus 54 days in the rehabilitation ward (reported difference 21 days, 95% CI 4 to 25 days; P = 0.018). Neumann 2004 reported the rehabilitation stay was not significantly different between the two groups (23.2 days versus 28.0 days; mean difference -4.80 days, 99% CI -12.29 to 2.69 days). Neumann 2004 also reported no significant difference in the destination at discharge between the two groups.

Espaulella 2000 found no difference between intervention and control groups for mobility or Barthel Index scores six months

after recruitment. Schürch 1998 also reported non-significant improvements in biceps muscle strength and activities of daily living score at six months; these were not reported as being measured by Tkatch 1992. Schürch 1998 reported that seven participants in the intervention group and 13 in the control group developed vertebral deformities after one year. Again denominators were not given, and the difference was said to be not statistically significant. Neumann 2004 found no significant difference between groups for the mobility subscale of the Functional Independence Measure at any time point including at three months post discharge.

Neither Schürch 1998 nor Tkatch 1992 gave information about the effect of the supplements on voluntary food intake. Espaulella 2000 reported that 64.7% (55/85) of the intervention group and 74.4% (64/86) of the control group had good consumption of the supplement. Neumann 2004 reported that participants had 19.8 days of the high-protein supplement, compared with 21.1 days for the lower-protein supplement. They found that energy intakes were not significantly different between the groups, but that the high-protein group also had significantly greater daily intakes of dietary fibre, vitamin C and polyunsaturated fatty acids.

### Vitamin supplements versus control

Day 1988 tested whether intravenous thiamin (vitamin B1) and other water soluble vitamins influenced postoperative mental function in participants. The daily dose of thiamin (250 mg) provided over 300 times the UK reference nutrient intake for this vitamin, that of riboflavin, 3.6 times, of pyridoxine, 42 times, of nicotinamide and ascorbic acid, 13 times. Sixty-one per cent of the intervention group and 75% of the control group had satisfactory thiamin status at baseline. There was no significant difference in mortality (*see* Analysis 5.1: RR 1.37, 99% CI 0.33 to 5.62) or in the numbers of participants with complications (see Analysis 5.2: RR 1.32, 99% CI 0.65 to 2.69). Likewise, the incidence of acute postoperative confusion, the primary outcome of Day 1988, did not differ between the two groups (11/28 versus 12/32; RR 1.05, 99% CI 0.45 to 2.44; analysis not shown). The length of hospital stay was not affected (mean difference 6.00 days, 99% CI -15.75 to 27.75 days), and residence at final follow-up was reported not to be affected by the intervention.

Hoikka 1980 compared oral 1-alpha-hydroxycholecalciferol (an active form of vitamin D) and 1 g calcium carbonate versus 20 g calcium carbonate in 37 participants with hip fracture. No data from main outcomes were reported, except for complications. Six, including two severe cases, out of 19 in the intervention group and two out of 18 in the control group developed hypercalcaemia (*see* Analysis 6.1: RR 2.84, 99% CI 0.41 to 19.48). Hoikka 1980 reported that there was no effect on hand muscle strength or bone mineral density (despite significant increases in bone alkaline phosphatase at three months suggesting healing) over the six months post-fracture observation period.

### Isonitrogenous ornithine alpha-ketoglutarate versus peptide supplements

Bean 1994, published only in abstract, investigated the effect of oral ornithine alpha-ketoglutarate, compared to an isonitrogenous peptide supplement, in 59 relatively undernourished older women with hip fracture. Unfortunately, no denominators for the intention-to-treat analyses were provided in the abstract, which reported that recruitment was slow and that compliance with the supplements for the full two months was poor. Bean 1994 reported that there was no difference in mortality (ornithine alpha-ketoglutarate supplemented 12.5%, control 11.1%, no denominators provided), compliance, duration of treatment or hospitalisation between the two groups. Bean 1994 reported there was no significant difference in complications but that major complications were significantly delayed in the intervention group (reported $P < 0.03$). No information was given in the abstract about the effect of the supplements on volitional food intake, although food diaries were kept.

### Dietetic assistants versus usual care

Duncan 2006 evaluated the use of dietetic assistants, who checked food preferences, helped order meals and supplements, provided feeding aids, assisted with food choice, and assisted with feeding at meal times. Mortality at four months was lower in the intervention group (*see* Analysis 7.1: RR 0.57, 99% CI 0.29 to 1.11) but the difference between the two groups ($P = 0.03$) was not statistically significant by our criteria ($P < 0.01$). The incidence of complications was similar in the two groups (*see* Analysis 7.2: RR 0.90, 99% CI 0.71 to 1.15). Duncan 2006 found no significant differences between the two groups in the lengths of stay in the acute ward (median 16 days versus 17 days; reported $P = 0.44$) or in hospital (34 days versus 32 days; reported $P = 0.81$). Using their own scoring scheme, Duncan 2006 reported that patient satisfaction was significantly greater in the intervention group at discharge (reported $P < 0.0001$). The mean daily energy intake was 349 kcal higher in the intervention group; this was mostly from supplements.

## DISCUSSION

### Summary of main results

This review has identified only very limited evidence for the benefit of nutritional supplementation after hip fracture. The variety of interventions and outcomes made data synthesis difficult. The failure to confirm an effect does not mean that there is no effect, but may simply reflect poor study design and inadequate size.

### Multinutrient supplementation

#### Oral supplements

Oral supplementation has no proven effect on post hip fracture mortality, but may possibly reduce 'unfavourable outcome' (death or complications). In previous versions of this review this outcome was statistically significant, but attention was drawn to the poor quality of the data. This is based on a very limited number of studies, and Delmi 1990 did not account for all the participants randomised. The effect of oral multinutrient supplementation on length of stay in hospital (acute and rehabilitation) is unclear. Administrative procedures, rather than the health of the patient may particularly influence this outcome.

#### Nasogastric tube feeding

No clear effect of nasogastric feeding is evident. The suggestion from Bastow 1983 that very thin patients may have reduced length of hospital stay requires confirmation. The high mortality in the intervention group in Hartgrink 1998 is unexplained, although the study appears to have been well conducted. Tube feeding was often poorly tolerated. One study of this group (Sullivan 1998) is unusual in that most of the trial participants were male, whereas most older people with hip fracture are female.

#### Nasogastric tube feeding and oral supplements

Tube feeding followed by oral supplementation has no proven effect on mortality or complications. Sullivan 2004, in which most trial participants were male, found that tube feeding was poorly tolerated.

#### Intravenous feeding and oral supplements

Eneroth 2006 found that a combination of intravenous feeding and oral supplements may reduce complications. However, intravenous feeding is an expensive, technically complex intervention which is usually reserved for people with non-functioning gastrointestinal tracts, which is unlikely in this group.

#### Nutritional status

There is no clear evidence to confirm that malnourished participants are more likely to benefit from multinutrient supplementation than those participants who are not malnourished.

### Increasing protein intake

A higher intake of protein may reduce the length of time spent in a rehabilitation hospital and numbers of complications, but has no proven effect on mortality. The studies are flawed by their failure to account for all participants. The results for mortality and 'unfavourable outcome' for Espaulella 2000 are contradictory and while many reasons for this, including that of random variation, can be put forward, none can be confirmed. There is weak evidence that including protein in the supplement improves rehabilitation.

### Other supplements

No evidence can be found from the two studies of Day 1988 and Hoikka 1980 to recommend the supplementation of vitamin B1 and other water soluble vitamins, or 1-alpha-hydroxycholecalciferol. Ornithine alpha-ketoglutarate, compared with an isonitrogenous peptide supplement, may delay the onset of complications post hip-fracture, but this is based on very weak evidence from one unpublished study (Bean 1994) and no significant difference in the incidence of complications was reported. No trials examined the effect of specific amino acid formulations.

### Dietetic assistants

The use of dietetic assistants was associated with lower trauma unit mortality in one trial. However, the difference between the two groups was not statistically significant by our criteria (99% confidence intervals for results from single trials). There were no statistically significant differences in the number of complications nor length of hospital stay. Duncan 2006 reported increased consumption of supplements and greater patient satisfaction in the intervention group. These favourable results (especially in terms of mortality) need to be checked in further randomised controlled trials.

## Overall completeness and applicability of evidence

Given that people with hip fracture are often malnourished, it is notable that this review gives no clear evidence that those who are malnourished are more likely to benefit from multinutrient supplementation than those who are not malnourished. The lack of a statistically significant difference in results of trials may be due not only to the small sample sizes, but also to the different definitions of malnutrition in individual trials. Quite possibly, people who are malnourished benefit more from nutritional supplementation, especially if they are severely malnourished, but more evidence is needed.

Incomplete compliance with nutritional supplementation was a major problem in these studies. Inability to tolerate nasogastric tubes and problems with palatability of oral feeds are common, particularly in confused, frail people. Malnutrition in itself produces mental apathy (Keys 1950), which may further reduce supplement intake. Ensuring increased nutritional intake thus has a major implication for nursing care, and has ethical implications when a person appears unwilling to feed or tolerate nasogastric feeding. While the combined intervention of nutritional supplementation and exercises tested in Miller 2006 was excluded from this review, the potential interaction between these two interventions merits further investigation.

Nasogastric feeding, if tolerated, allows the provision of higher supplements of energy (3.90 to 6.28 MJ, or 933 kcal to 1500 kcal daily, in the studies in this review), whereas oral supplements in the studies reviewed here generally provided under 2.51 MJ (600 kcal) daily. Thus nasogastric feeding, which potentially has more risk of complications, is likely to be targeted at those requiring higher levels of supplementation. Attempts to overcome the poor

palatability of oral supplements, and thus increase intakes further, include special high energy hospital meals and the provision of frequent, small snacks (Gall 1998). Related to this are other measures taken to encourage consumption of food by patients. For example, one of the excluded studies examined the effects of actively involving patients in their own dietary care, a procedure based on Salling's nursing model involving a dietary journal, information, guidance and instruction (Pedersen 1999). Dietetic assistants may be another way to increase food and supplement intake, as in the study by Duncan 2006, which requires examination in further research, including an economic evaluation.

Intravenous feeding used in Eneroth 2006 provided an additional 1000 kcal and 53 g protein daily, thus also allowing higher levels of supplementation. However, it also carries risks of fluid and electrolyte imbalance, hyperglycaemia and thrombophlebitis when delivered through a peripheral vein.

Nutritional supplementation should also be viewed in the context of general nutrition in hospitals. Given the high numbers of hip fracture patients with prior malnutrition, and the prolonged length of stay, it is surprising that nutrition, including the provision and uptake of basic foodstuffs, is often understated, or even overlooked, as a component of rehabilitative care programmes. Indeed, earlier guidelines for hip fracture management provided by the Scottish Intercollegiate Guidelines Network (SIGN 1997) failed to consider nutrition in rehabilitation; however, this omission was remedied subsequently (SIGN 2002).

There is interest in the hypothesis that nutritional supplementation may attenuate bone loss after fracture, which may also help to decrease the risk of further fractures (Schürch 1998a).

### Quality of the evidence

The studies are limited by inadequate sample size, failure to undertake intention-to-treat analysis (with frequent exclusion of participants for failing to take the supplements), failure to blind outcome assessors, failure to report and categorise participants' nutritional status, and inadequate period of follow-up with insufficient ascertainment of important outcomes.

### Potential biases in the review process

We think that it is unlikely that the review process itself has introduced bias. Our search, updated fully on a regular basis, is comprehensive and we actively pursue unpublished trials and data as well as ongoing and newly registered trials. We have used robust methodology, including independent trial selection and review of included trials, for the throughout the review and updating processes. Although we have not adopted risk of bias tables for this update, we have enhanced our methods in other ways including additional transparency for results not shown in the analyses.

### Agreements and disagreements with other studies or reviews

One review author (AA) has contributed to two more general systematic reviews of protein and energy supplementation in older people at risk from malnutrition (Milne 2006; Milne 2009). The above described limitations in the studies of this review also apply to nutritional intervention trials for other patient groups. Milne 2009 found that while there was no significant reduction in mortality in the supplemented compared with control groups overall, mortality results were statistically significant when limited to trials in which participants (N = 2461) were defined as undernourished. They concluded that there was a beneficial effect on complications but considered this needs confirmation. Despite the shared problem of malnutrition, the applicability of results from a more general population to people with hip fracture is still questionable and we consider that the focus of future research should remain on this particular patient group.

## AUTHORS' CONCLUSIONS

### Implications for practice

The strongest evidence of the effectiveness of nutritional supplementation exists for oral or oral and intravenous multinutrient feeds, but the evidence is still very weak. The benefits of nasogastric feeding are even less certain, and it should probably be reserved for the very malnourished, with extremely poor intakes not responsive to oral supplementation. Although tested in just one trial and needing confirmation, there is also weak evidence in favour of dietetic assistants.

### Implications for research

- Large, well-designed, adequately powered, trials of oral multinutrient supplementation, either by sip feeds and/or the hospital diet, are required, which should seek to be as inclusive of the patient population as possible. The provision of extra staff to help with feeding, e.g. dietetic assistants, should be explored further. Such trials should stratify allocation according to basic nutritional status to enable robust a priori subgroup analysis.

- Large, well-designed, adequately powered, trials of nasogastric or intravenous multinutrient supplementation should be conducted only in the most malnourished patients, where oral supplementation is unable to provide sufficient intake.

- The design and reporting of any future trial should conform to the CONSORT statement (Begg 1996; Moher 2001) or any future development of it.

- Future research should examine functional status (using standardised methods), the level of care required, compliance, patient perceived quality of life, and direct and indirect costs after hip fracture. These are in addition to mortality, individual complications and length of stay in hospital and rehabilitation. An independent observer should assess outcomes and the period of follow up should be at least one year.

Information on nutritional status and use of supplements should be collected in audits of hip fracture management. Such data could be used to investigate the relationship of nutritional status to outcome.

## ACKNOWLEDGEMENTS

For this version of the review we are grateful for the helpful comments at editorial and external review from: Mrs Lesley Gillespie, Prof William Gillespie, Prof Ronald Koretz and Prof Rajan Madhok.

We thank Dr Jose Botella-Carretero for providing information about his trial. We also thank Mrs Lindsey Elstub, Dr Joanne Elliott and Ms Amy Kavanagh from the Cochrane Bone, Joint and Muscle Trauma Group for their help.

We are grateful for the helpful comments at editorial and external review for previous versions of the review from the following: Dr Stuart Bruce, Ms Josephine Chow, Mrs Lesley Gillespie, Prof William Gillespie, Prof Adrian Grant, A/Prof Peter Herbison, Prof Ronald Koretz, Dr Vicki Livingstone, Prof Rajan Madhok, Prof Gordon Murray, Dr Martyn Parker, Prof Gwyn Seymour, Prof Marc Swiontkowski, Dr Arpana Verma and Dr Janet Wale. We also thank Prof Simon Allison, Ms Melinda Bopp, Dr Katrina Brown, Prof David Bruce, A/Prof Ian Cameron, Prof Maria Crotty, Dr Jonathan Day, Ms Donna Duncan, Ms Heidi Guyer, Dr Henk Hartgrink, Dr Ronald Houwing, Dr Antony Johansen, Prof Ronald Koretz, Dr Michelle Miller, Ms Megan Neumann, Dr Preben Pedersen, Dr Dennis Sullivan and Dr Jan Tidermark for providing further information about trials. We thank Ms Hilda Bastian for her help with the synopsis. We thank Prof Ronald Koretz for help with handsearching the Journal of Parenteral and Enteral Nutrition. We also thank Mrs Lesley Gillespie and Ms Leeann Morton from the Cochrane Bone, Joint and Muscle Trauma Group for their help.

Dr Alison Avenell's work on all versions of the review has been supported by the Medical Research Council, UK and The Chief Scientist Office of the Scottish Government Health Directorates.

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Avenell A, Handoll HHG. Nutritional supplementation for hip fracture aftercare in older people. *Cochrane Database of Systematic Reviews* 2005, Issue 2. [DOI: 10.1002/14651858.CD001880.pub3]

**Avenell 2006**

Avenell A, Handoll HHG. Nutritional supplementation for hip fracture aftercare in older people. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: 10.1002/14651858.CD001880.pub4]

* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Bastow 1983**

| | |
|---|---|
| Methods | Method of randomisation: quasi-randomised<br>Assessor blinding: unlikely<br>Intention-to-treat analysis: appears so<br>Lost to follow-up: appears none |
| Participants | Location: hospital, Nottingham, UK<br>Period of study: over 18 months, probably prior to 1983<br>122 participants<br>Inclusion criteria: hip fracture, mid-arm circumference or triceps skinfold, or both, one to two standard deviations below the mean (thin group) or over two standard deviations below the mean (very thin group)<br>Exclusion criteria: incapable of understanding study, severe dementia, serious concomitant physical disorder e.g. stroke<br>Sex: all female<br>Age: range 68-92 years<br>Fracture type: further details not given |
| Interventions | Timing of intervention: nasogastric feeding started within 5 days of surgery, 8 hours overnight with tube disconnected during the day, until discharge or death. Feeding stopped if participant did not tolerate tube or removed tube on 3 occasions<br>(a) 1 L Clinifeed Iso (4.2 MJ or 1000 kcal, 28 g protein, 270 mosmol/L) via fine bore nasogastric tube using peristaltic pump, and normal ward diet, with free access to snacks and drinks<br>(b) Normal ward diet, with free access to snacks and drinks<br>Allocated: 64/58<br>Assessed: 60/49 for independent mobility |
| Outcomes | Length of follow-up: until discharge or death<br>Main outcomes:<br>Mortality<br>Morbidity and complications: infection<br>Length of stay: hospital stay<br>Postoperative functional status: days to weight bearing with support, days to independent mobility<br>Putative side effects of treatment: aspiration, diarrhoea<br>Other outcomes:<br>Anthropometric indices: weight, triceps skinfold, mid-arm circumference<br>Nutritional indicators measured in blood: haemoglobin (*nr), albumin, thyroid binding prealbumin<br>Other nutritional: voluntary food intake<br>Patient compliance: tolerance of tube, duration of feeding |
| Notes | There was an administrative limit imposed of a maximum of 6 patients being fed at one time. Data presented from 1983 paper for numbers of participants are correct, error in number of participants in 1985 paper. Slight discrepancy with days to reach independent mobility presented in 1984 abstract. Reply from trialist (15/2/00) gave details of randomisation (on recall: either by date of admission or birth), outcome assessment, inclusion criteria, denominators and baseline comparability |

**Bastow 1983** (*Continued*)

| *Risk of bias* | | |
|---|---|---|
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | No | Quasi-randomised. On recall by trialist: "either on the basis of odd and even dates of birth or of admission". |

**Bean 1994**

| | |
|---|---|
| Methods | Method of randomisation: states double-blind, but no details<br>Assessor blinding: not reported<br>Intention-to-treat analysis: claimed by authors, but no details to support<br>Lost to follow-up: details not given |
| Participants | Location: hospitals; Nottingham, Leeds and Doncaster, UK<br>Period of study: recruitment over 2.5 years<br>59 participants<br>Inclusion criteria: fractured femur, 70-85 years, mean arm circumference < 25 cm, triceps skinfold < 18 mm<br>Exclusion criteria: other major medical disorder, failure to gain consent, demented (Cape score less than 9/12)<br>Sex: all female<br>Age: not given<br>Fracture type: further details not given |
| Interventions | Timing of interventions: start time unclear, twice daily for 2 months,<br>(a) Cetornan (ornithine a-ketoglutarate)20 g/d (0.293 MJ or 70 kcal, 2.73 g N), presumed orally<br>(b) Pro-up (defined formula peptide supplement, 0.293 MJ or 70 kcal, 2.73 g N), presumed orally<br>Allocated: ?/?<br>Assessed: ?/? |
| Outcomes | Length of follow-up: 6 months<br>Main outcomes:<br>Mortality<br>Morbidity and complications: all complications and delay in major complications (*nr)<br>Length of stay: duration of treatment or hospitalisation (*nr)<br>Postoperative functional status: fatigue score (*nr)<br>Other outcomes:<br>Anthropometric indices: arm muscle circumference (*nr)<br>Other nutritional: food intake (*nr)<br>Patient compliance: proportion completing 2 months' treatment (*nr) |
| Notes | Conference abstract only. No denominators for intention-to-treat analysis, so cannot use data in analysis. Data on arm muscle circumference, fatigue score and food intake presented for 35 participants completing 2 months of treatment. Request for further details (including denominators)sent 19/5/99, resent 4/2/00 |

*Risk of bias*

**Bean 1994** (*Continued*)

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | "randomized in a double-blind fashion" |

**Botella-Carretero 2008**

| | |
|---|---|
| Methods | Method of randomisation: sealed opaque envelopes, prepared independently from recruitment<br>Assessor blinding: not done<br>Intention-to-treat analysis: unclear<br>Lost to follow-up: details given |
| Participants | Location: Hospital Ramon y Cajal, Madrid, Spain<br>Period of study: February 2006 to February 2007<br>90 participants<br>Inclusion criteria: > 65 years, surgery for hip fracture, written informed consent.<br>Exclusion criteria: weight loss > 5% in previous month or > 10% in previous 6 months, and/or albumin < 27 g/dL. Acute or chronic renal failure, hepatic insufficiency or cirrhosis (Child B or C), severe heart failure (New York heart classification III or IV), respiratory failure, gastrointestinal condition precluding adequate oral intake. Also: previous oral nutrition supplements or nutrition support in previous 6 months.<br>Sex: 71 female, 19 male<br>Age: mean age 84 years<br>Fracture type: not given |
| Interventions | Timing of intervention: started 48 hours after operation, until hospital discharge<br>(a) Four 10 g packets a day of Vegenat-med Proteina (Vegenat SA, Badajoz, Spain) each providing 9 g protein and 38 kcal, dissolved in water, milk or soup from diet.<br>(b) Two 200 ml bricks a day (Resource Hiperproteico, Novartis Medical Nutrition, Barcelona)providing total of 37.6 g protein and 500 kcal.<br>(c) no oral nutrition supplements.<br>Allocated: 30/30/30<br>Assessed: 28/30/27 |
| Outcomes | Length of follow-up: up to hospital discharge<br>Main outcomes:<br>Mortality<br>Complications: urinary, respiratory, wound infection; pressure ulcer, dysphagia, ischaemic heart disease; severe hyponatraemia; anaphylaxis; vomiting and/or diarrhoea<br>Length of acute hospital stay<br>Level of care: time to mobilisation<br>Other outcomes:<br>Other nutritional: energy and protein intake |
| Notes | Emailed 22nd January 2009 requesting mortality information. Author replied 23rd January confirming no participants had died during the trial. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|

**Botella-Carretero 2008** (*Continued*)

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|---|---|---|
| Allocation concealment? | Yes | Use of "sealed opaque envelopes". Independent preparation of envelopes: "The investigator recruiting the patients ....had no role in the randomisation process". |

**Brown 1992**

| | |
|---|---|
| Methods | Method of randomisation: alternating numbers<br>Assessor blinding: blinded<br>Intention-to-treat analysis: carried out<br>Lost to follow-up: no losses to follow-up |
| Participants | Location: hospital, Ipswich, UK<br>Period of study: six months, probably prior to 1992<br>10 participants<br>Inclusion criteria: thin (based on weight for height, triceps skinfold, mid-arm circumference - two out of three more than one standard deviation below reference mean), elderly, females with hip fracture<br>Exclusion criteria: malignant disease, mental illness, renal or hepatic failure, neurological disorder, stroke, diabetes<br>Sex: all female<br>Age: not given, but "elderly"<br>Fracture type: trochanteric or subcapital hip fracture |
| Interventions | Timing of intervention: from second day of admission until discharge (including rehabilitation hospital)<br>(a) Participant offered oral nutritional supplement Fresubin (Fresenius)calculated to make up deficit between intake from normal hospital diet and requirement. Fresubin provides 4.2 kJ or 1 kcal/ml, as 15% protein energy, 30% fat energy and 55% carbohydrate energy<br>(b) Normal hospital diet<br>Allocated: 5/5<br>Assessed: 5/5 |
| Outcomes | Length of follow-up: no details (21+ days)<br>Main outcomes:<br>Mortality<br>Morbidity and complications: pressure sore (*nr)<br>Length of stay: days to discharge from orthopaedic surgeon<br>Postoperative functional status: two stage walking goals<br>Other outcomes:<br>Anthropometric indices: percentage losses in weight, triceps skinfold, midarm circumference, arm muscle circumference<br>Nutritional indicators measured in blood: albumin, prealbumin, zinc, magnesium (all *nr)<br>Other nutritional: dietary intake (*nr) |
| Notes | Author provided protocol of trial and information on method of randomisation and outcome assessment.<br>Request for further details (other outcomes, period of follow-up)sent 19/5/99, resent 3/2/00 |

***Risk of bias***

**Brown 1992** (*Continued*)

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | No | Alternating numbers (information from trial author). |

**Bruce 2003**

| | |
|---|---|
| Methods | Method of randomisation: quasi-randomised by year of birth<br>Assessor blinding: not reported<br>Intention-to-treat analysis: unclear (though likely)<br>Lost to follow-up: no withdrawals but some unaccounted "missing data points" |
| Participants | Location: hospital, Freemantle, Australia<br>Period of study: patients admitted June 1998 to December 1999<br>109 participants<br>Inclusion criteria: women with hip fracture, consent given<br>Exclusion criteria: BMI <20 or >30 kg/m2, nursing home resident, resident outside metropolitan Perth ( preventing follow up), diseases expected to influence nutritional intake (malignancy, severe organ failure), diabetes (to avoid potential hyperglycaemia), fracture due to major trauma<br>Sex: 109 female<br>Age: mean 84 years<br>Fracture type: further details not given |
| Interventions | Timing of intervention: started within 2 to 3 days after surgery, for 28 days<br>(a) One 235 ml can of Sustagen Plus daily (Mead Johnston), providing 352 kcal or 1.47 MJ, 17.6 g protein, 11.8 g fat, 44.2 g carbohydrate, 376 mcg retinol equivalents, 1.2 mcg vitamin D, 2.4 mg vitamin E, 15 mg vitamin C, 0.4 mg thiamin, 0.5 mg riboflavin, 8.7 mg niacin, 0.6 mg vitamin B6, 0.9 mcg vitamin B12, 71 mcg folate, 1.9 mg pantothenic acid, 14 mcg biotin, 259 mg sodium, 491 mg potassium, 371 mg chloride, 263 mg calcium, 261 mg phosphorus, 3.8 mg iron, 106 mg magnesium, 3.8 mg zinc, 41 mcg iodine, 0.4 mg copper, 0.6 mg manganese, 19 mcg selenium, 19 mcg chromium, 47 mcg molybdenum; chocolate and vanilla flavours. Dietitian carried out preliminary taste test and offered encouragement and strategies to help with compliance, e.g. ways to alter taste and timing of supplement. And routine care<br>(b) Routine care<br>Allocated: 50/59<br>Assessed: ?/? |
| Outcomes | Length of follow-up: 6 months<br>Main outcomes:<br>Mortality: combined outcome with need for nursing home<br>Length of stay: hospital<br>Postoperative functional status: % with fall in Katz score<br>Level of care and extent of support required after discharge: % discharged home, % home at 6 months<br>Other outcomes:<br>Anthropometric indices: weight<br>Nutritional indicators in blood: albumin<br>Patient compliance: consumption of cans of supplement |

**Bruce 2003** (*Continued*)

| | |
|---|---|
| Notes | Percentages provided in report indicate variation in denominators used. Requests for further details of denominators and deaths during study sent 13/8/03 and 13/10/03. Reply received October 2003 giving details of denominators, deaths, withdrawals, and details of vitamin and mineral content of supplement |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | No | "Quasi-randomisation of cases was carried out using their date of birth." |

**Day 1988**

| | |
|---|---|
| Methods | Method of randomisation: computer-generated random sequence, insufficient indication of adequate safeguards<br>Assessor blinding: blinded assessment of mental state, other outcomes not stated<br>Intention-to-treat analysis: analysis performed<br>Lost to follow-up: details given |
| Participants | Location: hospital, Cardiff, UK<br>Period of study: recruitment over six months, probably prior to 1988<br>60 participants<br>Inclusion criteria: people with acute proximal femur fracture, age 60+years<br>Exclusion criteria: unable to be assessed preoperatively, not seen within 24 hours of admission, pathological fracture, difficulty obtaining consent from patient or relative<br>Sex: 44 female, 16 male<br>Age: 60 years and older (inclusion criterion)<br>Fracture type: 17 cervical, 9 trochanteric, 2 other/16 cervical, 14 trochanteric, 2 other |
| Interventions | Timing of intervention: Two doses of vitamin preparation given preoperatively, and then one dose daily for five postoperative days<br>(a) Intravenous Parentrovite IVHP (containing 250 mg thiamine hydrochloride, 4 mg riboflavine, 50 mg pyridoxine, 160 mg nicotinamide, 500 mg ascorbic acid, 1 g anhydrous dextrose)<br>(b) No supplement<br>Allocated: 28/32<br>Assessed: 28/32 for abbreviated mental test at day 2 |
| Outcomes | Length of follow-up: 3 months<br>Main outcomes:<br>Mortality<br>Morbidity and complications: total number of complications, numbers of participants with complications<br>Length of stay: hospital<br>Postoperative functional status: acute confusional state, acute on chronic confusional state, abbreviated mental test, objective learning test, Ishihara Colour Plates<br>Care required after discharge: final placement<br>Putative side effects of treatment: serious and other adverse events<br>Other outcomes:<br>Nutritional indicators measured in blood: thiamine status by thiamine pyrophosphate activation of red |

**Day 1988** (*Continued*)

| | |
|---|---|
| | cell transketolase |
| Notes | Request for further details (method of randomisation, constituents of Parentrovite IVHP, other outcomes) sent. Reply from trialist (27/5/99) gave details of the intervention, and information on fracture type, baseline albumin levels, complications and hospital stay |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | "Allocation of patients was based on randomly generated numbers". However, no indication of adequate safeguards for allocation concealment. |

**Delmi 1990**

| | |
|---|---|
| Methods | Method of randomisation: not stated<br>Assessor blinding: not reported<br>Intention-to-treat analysis: appears intention to treat, but denominators unclear<br>Lost to follow-up: deaths reported, but unclear if other losses to follow-up |
| Participants | Location: orthopaedic unit in hospital and recovery hospital, Geneva, Switzerland<br>Period of study: 1 March to 15 May 1985<br>59 participants<br>Inclusion criteria: femoral neck fracture after an accidental fall, aged over 60 years<br>Exclusion criteria: fracture from violent external trauma, pathological fracture due to tumour or non-osteoporotic osteopathy; overt dementia; renal, hepatic, or endocrine disease; gastrectomy or malabsorption; taking phenytoin, steroids, barbiturates, fluoride or calcitonin<br>Sex: 53 female, 6 male<br>Age: mean age 82 years<br>Fracture type: 26 femoral neck, 33 inter-trochanteric |
| Interventions | Timing of intervention: from admission to orthopaedic unit to end of stay in second (recovery) hospital, supplement given once daily at 20.00 hours for a mean period of 32 days.<br>(a) 250 ml oral nutritional supplement (1.06 MJ or 254 kcal, 20.4 g protein, 29.5 g carbohydrate, 5.8 g lipid, 525 mg calcium, 750 IU vitamin A, 25 IU vitamin D3, nicotinamide, folate, calcium pantothenate, biotin, minerals; and vitamins E, B1, B2, B6, B12, C) and standard hospital diet<br>(b) Standard hospital diet<br>Allocated: 27/32<br>Assessed: ?25/?27 at 6 months |
| Outcomes | Length of follow-up: 6 months<br>Main outcomes:<br>Mortality<br>Morbidity and complications: complications (total, bedsore, severe anaemia, cardiac failure, infection, gastrointestinal ulcer, other), favourable clinical course (excludes death, major complication, or two or more minor complications)<br>Length of stay: orthopaedic unit and recovery hospital |

**Delmi 1990** (*Continued*)

| | |
|---|---|
| | Other outcomes:<br>Nutritional indicators measured in blood: albumin, transferrin (*nr)<br>Other nutritional: energy, protein and calcium intake |
| Notes | Numbers of complications unclear, request for further details sent 24/5/99, resent 7/2/00 |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | No information. Just "randomised". |

**Duncan 2006**

| | |
|---|---|
| Methods | Method of randomisation: sequentially numbered opaque sealed envelopes, initially in blocks of 20, later reduced to blocks of 10, prepared by member of staff outside trial, opened sequentially<br>Assessor blinding: appears so<br>Intention-to-treat analysis: post-randomisation exclusion of people for conservative care of hip fracture<br>Lost to follow-up: details given |
| Participants | Location: single trauma ward, University Hospital of Wales, Cardiff, UK<br>Period of study: recruitment May 2000 to August 2003<br>318 participants<br>Inclusion criteria: women aged over 65 years presenting to trauma ward with acute nonpathological hip fracture, consent or assent to trial<br>Exclusion criteria: none<br>Sex: all female<br>Age: mean age 84 years<br>Fracture type: not given |
| Interventions | Timing of intervention: unclear when commenced, during stay in acute trauma ward, median 16-17 days. Dietetic assistant present on ward 6 hours/day for 7 days a week<br>(a) additional attention of dietetic assistant (previous NHS experience, given 14 day period of orientation and training), working closely with specialist dietitian. Asked to ensure participants met nutritional needs, including by: checking personal and cultural food preferences; co-ordinating appropriate meal orders with catering staff; ordering nutritional supplements; provision of feeding aids; assisting with food choice, portion size and positioning at mealtimes; sitting with, encouraging and feeding; collecting information to aid nutritional assessment by dietitian<br>(b) Nurse and dietitian led care, including routine provision of oral nutritional supplements to all participants<br>Allocated: 153/165<br>Assessed: 145/157 for mortality |
| Outcomes | Length of follow-up: 4 months<br>Main outcomes:<br>Mortality<br>Morbidity and complications: on trauma ward in survivors<br>Length of trauma ward and hospital stay |

**Duncan 2006** (*Continued*)

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|---|---|
| | Other outcomes:<br>Changes in anthropometric indices: weight, mid-arm circumference, triceps skinfold<br>Changes in nutritional indicators measured in blood: albumin, lymphocyte count<br>Functional markers of nutritional status: hand grip strength<br>Other nutritional: energy intake |
| Notes | Request for further details on participants with complications sent 15/3/06. Reply from trialist (15/3/06) provided number and per cent of live participants having had complications on trauma ward.<br>A letter to the editor in Age and Ageing Advance Access (June 24, 2006) by Hewitt and Torgerson pointed out the numerical difference between the two groups was higher than expected given the reported block size of 10. The reply from Duncan indicated that they initially started the study with a block size of 20. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | "Randomisation was by sequentially numbered, opaque, sealed envelope method in blocks of 10, prepared by a member of staff not directly involved in the trial." |

**Eneroth 2006**

| | |
|---|---|
| Methods | Method of randomisation: block randomisation conducted by research nurse, using closed, numbered envelopes<br>Assessor blinding: no<br>Intention-to-treat analysis: appears so<br>Lost to follow-up: details given |
| Participants | Location: department of orthopaedics, Lund University Hospital, Lund, Sweden<br>Period of study: before August 2005<br>80 participants<br>Inclusion criteria: over 60 years with a cervical or trochanteric hip fracture, written informed consent, surgery < 48 hours from trauma.<br>Exclusion criteria: multiple fractures, pathological fractures, malignancy, inflammatory joint disease, pain or functional impairment other than hip fracture which might hamper mobilization, dementia, depression, acute psychosis, known alcohol or medication abuse, epilepsy, mini-mental test score < 6, warfarin, insulin-treated diabetes; heart, kidney ore liver insufficiency, suspected acute myocardial infarction, haematemesis.<br>Sex: 63 female, 17 male<br>Age: mean age 81 years<br>Fracture type: 45 cervical, 35 trochanteric |
| Interventions | Timing of intervention: first 10 days in hospital<br>(a) 1000 ml Vitrimix (Kabi Pharmacia AB, Sweden) intravenously (amino acids, fat, carbohydrate, electrolytes daily for 3 days (100 kcal, 53 g protein daily), then 7 days oral Fortimel 400 ml (400 kcal.day; Nutricia AB, Netherlands). Trace elements (Tracel, Kabi Pharmacia AB), water and fat soluble vitamins (Soluvit Novum and Vitalipid Novum, Kabi Pharmacia AB) were added to Vitrimix.<br>(b) Usual hospital diet. |

**Eneroth 2006** (*Continued*)

| | |
|---|---|
| | Allocated: 40/40<br>Assessed: 40/40 for mortality |
| Outcomes | Length of follow-up: mean of 120 days<br>Main outcomes:<br>Mortality<br>Complications: wound infection, pneumonia, urinary infections, thrombophlebitis, deep vein thrombosis, pulmonary embolism, pulmonary oedema, myocardial infarction<br>Length of acute hospital stay<br>Level of care: discharge to own home<br>Other outcomes:<br>Other nutritional: energy intake, fluid intake |
| Notes | Emailed on 22nd January 2009 in an attempt to clarify denominators. Author replied 10th February confirming denominators. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | "A research nurse (UBO) randomized 80 patients to either a control or an intervention group using block randomization with 40 closed and numbered envelopes in each block." |

**Espaulella 2000**

| | |
|---|---|
| Methods | Method of randomisation: computer generated assignment, balanced in blocks of four, with sealed envelopes, opened by pharmacist<br>Assessor blinding: blinded<br>Intention-to-treat analysis: 10 excluded: 8 excluded for protocol violation and 2 excluded because they could not swallow - intention-to-treat analysis not possible<br>Lost to follow-up: details given |
| Participants | Location: Hospital General de Vic, Barcelona<br>Period of study: July 1994 to July 1996<br>171 participants<br>Inclusion criteria: hospitalised for fracture of the proximal femur, aged 70 years and over<br>Exclusion criteria: advanced dementia, needing intravenous nutrition, pathological fracture, fracture not due to accidental fall<br>Sex: 135 female, 36 male<br>Age: mean 82.6 years<br>Fracture type: 115 extracapsular, 56 intracapsular hip fractures |
| Interventions | Timing of intervention: begun within 48 hours of study entry, consumed once daily at night for 60 days<br>(a) 200 ml oral supplement in 3 flavours (0.62 MJ or 149 kcal, 20 g protein, 1.5 g carbohydrate, 7 g fat, 800 mg calcium, 3 IU vitamin A, 1.7 mg thiamin, 2.02 mg riboflavin, 2.25 mg pyridioxine, 5.5 mcg vitamin B12, 122.25 mg vitamin C, 25 IU vitamin D3, 10 mg calcium pantothenate, 16.87 mg vitamin |

**Espaulella 2000** (*Continued*)

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|---|---|
| | E, 0.45 mg biotin, 500 mcg folic acid, 22.5 mg nicotinamide), prepared by pharmaceutical company (Clinical Nutrition S.A., Spain)<br>(b) 200 ml oral supplement in 3 flavours (0.65 MJ or 155 kcal as 25.3 g carbohydrate and 6 g fat), prepared by pharmaceutical company<br>Allocated: 85/86<br>Assessed: 61/67 for all outcomes |
| Outcomes | Length of follow-up: 6 months<br>Main outcomes:<br>Mortality: all cause and related to fracture, days between fracture and death (survival curve)<br>Morbidity and complications: including delirium, bed sore, urinary tract infection<br>Length of stay: acute hospital ward<br>Postoperative functional status: Barthel Index, Mobility Index, days from surgery to walking<br>Level of care and extent of support required after discharge: discharge home or geriatric rehabilitation unit, use of walking aids at 6 months<br>Other outcomes:<br>Nutritional indicators measured in blood: albumin<br>Patient compliance |
| Notes | Request for further details (including follow-up data on excluded participants, details of supplement) sent 14/2/00 and 6/6/00. Replies from Guyer (6/3/00 and 13/6/00) confirmed assessor blinding, gave other details of methodology and contents of supplement, as well as details of outcome of the excluded participants. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | Computer generated assignment, balanced in blocks of four, with sealed envelopes, prepared by epidemiology unit. "Upon being advised of a patient's inclusion, the pharmacist assigned the patient a study number and opened the envelope ..." |

**Gallagher 1992**

| | |
|---|---|
| Methods | Method of randomisation: not stated<br>Assessor blinding: not reported<br>Intention-to-treat analysis: not reported<br>Lost to follow-up: not reported |
| Participants | Location: hospital, Cincinnati, USA<br>Period of study: over 15 months<br>97 participants<br>Inclusion criteria: people with hip fracture having surgery, serum albumin < 3.5 g/dL on admission<br>Exclusion criteria: no details<br>Sex: male and female, numbers not given<br>Age: not given |

**Gallagher 1992** (*Continued*)

| | |
|---|---|
| | Fracture type: not given |
| Interventions | Timing of intervention: tube placed in surgery, supplementary feeding began first post-operative night, 11 hours per night, continued until participant ate 75% of their calorie needs for 3 consecutive days<br>(a) Small-bore nasogastric tube providing 3.90 MJ or 933 kcal, 33 g protein each night; normal diet and snacks<br>(b) Normal diet and snacks<br>Allocated: ?/?<br>Assessed: ?/? |
| Outcomes | Length of follow-up: no details (21+ days)<br>Main outcomes:<br>Morbidity and complications: surgical and gastrointestinal<br>Length of stay: rehabilitation stay<br>Postoperative functional status: days to meet physical therapy goals<br>Other outcomes:<br>Nutritional indicators measured in blood: albumin and transferrin |
| Notes | Conference abstract with no denominators, so cannot use data in analysis. Notes taken by Ronald Koretz of an oral conference presentation by Gallagher indicated a quasi-randomised study with dropouts being placed in control group; thus denominators remain unclear. The notes gave details of total length of stay, numbers pulling out nasogastric tube, deaths, and medical and surgical complications.<br>Request for further details (including denominators)sent 26/2/99, resent 3/2/00 |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | No information: "randomized". |

**Hankins 1996**

| | |
|---|---|
| Methods | Method of randomisation: sealed, opaque envelopes in blocks of 10, appears stratified by place of residence<br>Assessor blinding: not done<br>Intention-to-treat analysis: carried out<br>Lost to follow-up: details given |
| Participants | Location: acute care in Hornsby-Kuringai Hospital and rehabilitation hospitals, Sydney, Australia<br>Period of study: admissions from 16 May to 8 August 1996<br>32 participants<br>Inclusion criteria: fractured neck of femur after accidental fall; admitted from home, hostel or nursing home; age 65 years or older; mid-upper arm circumference less than or equal to 25th centile for sex and age<br>Exclusion criteria: malignancy, chronic renal failure, hepatic disease, no consent from patient or next of kin, did not reside locally, not notified of admission, unstable diabetes<br>Sex: 27 female, 5 male<br>Age: mean 86 years<br>Fracture type: not given |

**Hankins 1996** (*Continued*)

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|---|---|
| Interventions | Timing of intervention: started within 5 days of surgery, given once in the morning and once in the evening for 30 days, served on meal tray in hospital by nurses, given by family or self-administered out of hospital<br>(a) Oral supplement of 250 ml Sustagen twice daily (total daily intake 22.5 g protein, 10 g fat, 60 g carbohydrate, 1.712 MJ or 409 kcal energy, 500 mcg vitamin A, 6.6 mcg vitamin D, 50.8 mg vitamin C, 1.2 mg thiamin, 1.15 mg riboflavin, 13 mg niacin, 1.3 mcg vitamin B12, 825 mg calcium, 670 mg phosphorus, 8 mg iron, 66 mcg iodine, 1.2 g potassium, 370 mg sodium) plus standard hospital diet<br>(b) Standard hospital diet<br>Allocated: 17/15<br>Assessed: 17/14 |
| Outcomes | Length of follow-up: 2 months<br>Main outcomes:<br>Mortality<br>Morbidity and complications: complications (total, infection, pressure sores, pulmonary embolism, delirium, anaemia, cardiac failure, acute renal failure), favourable clinical course (excludes death, major complication, or two or more minor complications)<br>Length of stay:acute hospital, rehabilitation hospital, and total stay<br>Postoperative functional status: Barthel Index<br>Care required after discharge: place of residence at two months<br>Other outcomes:<br>Anthropometric indices: self-reported weight, mid-upper arm circumference<br>Other nutritional: energy, protein intakes from food and supplement; calcium, iron and vitamin C intakes from food<br>Patient compliance: numbers completing full 30 days of supplement |
| Notes | Request for further details (blinding of outcome assessors, details of supplement administration, further information on outcomes) sent. Reply from trialist (11/6/99) gave details of outcome assessor blinding, supplement administration and outcomes |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | "Sealed, numbered opaque envelopes in blocks of 10". Information from Ian Cameron |

**Hartgrink 1998**

| | |
|---|---|
| Methods | Method of randomisation: computer generated randomisation list. Use of numbered envelopes.<br>Assessor blinding: no, but statistician appeared blinded<br>Intention-to-treat analysis: attempted, but 11 randomised participants subsequently excluded for not fulfilling entry criteria<br>Lost to follow-up: details given |
| Participants | Location: teaching hospital, The Hague, The Netherlands<br>Period of study: May 1993 to November 1995<br>140 participants |

**Hartgrink 1998** (*Continued*)

| | |
|---|---|
| | Inclusion criteria: hip fracture, pressure sore risk score of 8 or above (out of a possible 30), gave consent<br>Exclusion criteria: pressure sores of grade 2 (blister formation)or more at admission<br>Sex: 122 female, 18 male<br>Age: mean 83.6 years<br>Fracture type (of 129): 60 medial, 15 lateral, 53 trochanteric, 1 other hip fracture |
| Interventions | Timing of intervention: nasogastric tube placed during surgery or within 12 hours afterwards. Feeding started within 24 hours of surgery. Intended duration of feeding 2 weeks. Feed administered between 21.00 hours and 05.00 hours to minimise interference with standard hospital diet.<br>(a) Nasogastric tube feed of 1 L Nutrison Steriflo Energy-plus ( 340 mosmol/L, 6.28 MJ or 1500 kcal, 60 g protein, 184 g carbohydrate, 58 g fat, 800 mg sodium, 1350 mg potassium, 1250 mg chloride, 570 mg calcium, 570 mg phosphate, 200 mg magnesium, 10 mg iron, 10 mg zinc, 1.5 mg copper, 3 mg manganese, 1 mg fluoride, 50 mcg molybdenum, 43 mcg selenium, 33 mcg chromium, 0.1 mg iodide, 670 mcg retinol equivalents, 5 mcg vitamin D, 8.1 mg alpha tocopherol, 40 mcg vitamin K, 1 mg thiamin, 1.1 mg riboflavin, 26 mg niacin, 4 mg pantothenic acid, 1.3 mg vitamin B6, 130 mcg folic acid, 2 mcg vitamin B12, 100 mcg biotin, 50 mg vitamin C, 200 mg choline) plus normal hospital diet. If participant removed tube, replaced a maximum of 3 times.<br>(b) Standard hospital diet<br>Allocated: 70/70<br>Assessed: 48/53 |
| Outcomes | Length of follow-up: 2 weeks<br>Main outcomes:<br>Mortality<br>Morbidity and complications:clinically relevant pressure sore<br>Length of stay: numbers discharged at 1 and 2 weeks<br>Putative side effects of treatment: aspiration pneumonia<br>Other outcomes:<br>Nutritional indicators measured in blood: haemoglobin, albumin<br>Other nutritional: energy and protein intakePatient compliance: compliance with tube feeding |
| Notes | Request for further details (including supplement details and administration, randomisation process, blinding of outcome assessors, details of 11 post-randomised participants excluded, other outcomes) sent. Reply from trialist (23/6/99) gave baseline details on all participants randomised, method of randomisation, assessor blinding, supplement details and administration. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | "Randomisation list prior to trial was made by computer". "If informed consent a numbered envelope was opened". No information on adequate safeguards. |

**Hoikka 1980**

| | |
|---|---|
| Methods | Method of randomisation: quasi-randomised by date of birth<br>Assessor blinding: not reported<br>Intention-to-treat analysis: not reported<br>Lost to follow-up: not reported, but incomplete outcome ascertainment |
| Participants | Location: hospital, Kuopio, Finland<br>Period of study: probably prior to 1980<br>37 participants<br>Inclusion criteria: hip fracture caused by moderate or no trauma<br>Exclusion criteria: under 50 years, renal disease, poor co-operation, clinically evident osteomalacia<br>Sex: 29 female, 8 male<br>Age: mean 74 years, range 55 to 86 years<br>Fracture type: further details not given |
| Interventions | Timing of intervention: start time unclear, four months treatment.<br>(a) 1 mcg 1-alpha-hydroxycholecalciferol and 1 g calcium as calcium carbonate daily<br>(b) Placebo and 1 g calcium as calcium carbonate daily<br>Allocated: 19/18<br>Assessed: 13/15 at six months for muscle strength |
| Outcomes | Length of follow up: 6 months<br>Main outcomes:<br>Putative side effects of treatment: hypercalcaemia<br>Other outcomes:<br>Bone mineral density<br>Functional markers of nutritional status: hand muscle strength |
| Notes | Request for further details (timing of intervention, denominators for some outcomes) sent 11/5/99, returned to sender. Details on method of randomisation received from Jane Robertson on 02/02/1999. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | No | Quasi-randomised by date of birth (see Notes) |

**Houwing 2003**

| | |
|---|---|
| Methods | Method of randomisation: use of a computer programme, balanced in blocks of four, by independent person<br>Assessor blinding: nurse assessment blinded, but report states that supplements were "not exactly identical"<br>Intention-to-treat analysis: probably - appears so<br>Lost to follow-up: probably none |
| Participants | Location: three centres, Arnhem, Deventer and Nieuwegein, in The Netherlands<br>Period of study: April 1998 to December 1999<br>103 participants<br>Inclusion criteria: hip fracture, pressure ulcer score >8 (Dutch Consensus Meeting scoring system), consent |

**Houwing 2003** (*Continued*)

| | |
|---|---|
| | from patient or legal representative<br>Exclusion criteria: terminal care, metastatic hip fracture, insulin-dependent diabetes, renal disease, hepatic disease, morbid obesity (BMI > 40), therapeutic diet incompatible with supplementation, pregnancy, lactation<br>Sex: 84 female, 19 male<br>Age: mean age 81 years<br>Fracture type: not given (48 internal fixation, 44 hemi-arthroplasty) |
| Interventions | Timing of intervention: supplemented from immediately post-operative period for four weeks or until discharge, given between regular meals<br>(a) 400 ml/day oral supplement (600 kcal or 2.51 MJ, 40 g protein, 6 mg arginine, 20 mg zinc, 500 mg vitamin C, 200 mg vitamin E as alpha-tocopherol, 4 mg carotenoids (Cubitan, NV Nutricia, The Netherlands)); and regular diet<br>(b) Placebo supplement was a non-caloric, water-based drink with sweeteners, colourants and flavourings in similar packaging, look and taste not identical to active supplement; and regular diet<br>Allocated: 51/52<br>Assessed: 51/52 |
| Outcomes | Length of follow-up: 28 days or earlier if discharged<br>Main outcomes:<br>Morbidity and complications: pressure sores<br>Other outcomes:Patient compliance: mean percentage intake/day, days supplemented |
| Notes | Request for further details (method of randomisation, other complications, adverse events, length of stay, further details of supplement)sent 13/10/03.<br>Details of randomisation method received 29/10/03. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | Use of a computer programme, balanced in blocks of four, by an independent person. Information from trialist. |

**Madigan 1994**

| | |
|---|---|
| Methods | Method of randomisation: not stated<br>Assessor blinding: not reported<br>Intention-to-treat analysis: not carried out, results presented for 30 participants of 34 randomised, results from the two supplemented groups were combined<br>Lost to follow-up: details given |
| Participants | Location: Illawarra Regional Hospital, Port Kembla Campus, Woolongong, Australia<br>Period of study: admissions from 6 September to 6 December 1993, 7 February to 31 March 1994<br>34 participants<br>Inclusion criteria: femoral neck fracture resulting from an accidental fall, age over 60 years, informed consent |

**Madigan 1994** (*Continued*)

| | |
|---|---|
| | Exclusion criteria: pathological fracture due to tumour; fracture due to violent external trauma; elective total hip replacement; renal, hepatic, metastatic or endocrine (affecting skeletal metabolism)disease; admitted from nursing home; failure to gain consent; transferred to another hospital for surgery<br>Sex: 22 female, 8 male, of 30<br>Age: all over 60 years<br>Fracture type: further details not given |
| Interventions | Timing of intervention: started on admission for 10 days, once daily after evening meal<br>(a) 250 ml oral supplement prepared by dietitian from ProMod (protein powder) and Polyjoule (glucose polymer) providing 1.30 MJ or 310 kcal; 16 g protein, 41.4 g carbohydrate, 9.2 g fat, 0.19 mg riboflavin, 245 mg calcium, phosphorus 171 mg, and standard hospital diet.<br>(b) One multivitamin/mineral tablet daily (ELEVIT RDI, Roche) providing 750 mcg vitamin A, 1.1 mg thiamin, 1.7 mg riboflavin, 20 mg nicotinamide, 7 mg pantothenic acid, 1.9 mg pyridoxine, 2 mcg vitamin B12, 200 mcg biotin, 200 mcg folic acid, 30 mg vitamin C, 200 IU vitamin D3, 15 IU vitamin E, 125 mg calcium, 100 mg magnesium, 125 mg phosphorus, 5 mg iron, 1 mg copper, 1 mg manganese, 7.5 mg zinc 250 ml), plus oral supplement as above, and standard hospital diet<br>(c) Standard hospital diet<br>Allocated: ?/?/?<br>Assessed: 18/12 (a+b/c) |
| Outcomes | Length of follow-up: 3 months post-discharge<br>Main outcomes:<br>Mortality<br>Morbidity and complications - numbers of complications (urinary infections, wound infections/delayed healing, pressure sores, pneumonia, deep venous thrombosis, sepsis)<br>Length of stay: acute hospital<br>Postoperative functional status: number transferred to rehabilitation hospital, days to reach partial or full weight bearing with support, days to reach independent mobility<br>Care required after discharge: discharge to home, hostel, nursing home, number of subjects returning to pre-morbid mobility<br>Other outcomes:<br>Anthropometric indices: mid-upper arm circumference (*nr), triceps skinfold (*nr)<br>Nutritional indicators measured in blood: total lymphocyte count (*nr), albumin (*nr)<br>Other nutritional: total energy, protein, vitamin and mineral intakes from food and supplements<br>Patient compliance: number taking protein supplement for only 7 days |
| Notes | In the trial report, the two supplemented groups were combined for analysis for comparison with control group. Three subjects eliminated post-randomisation from analysis because only took protein supplement for 7 days, and one eliminated for developing diabetes. Numbers of participants assigned/assessed not always clear. Request for further details sent 4/2/00 |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | No information: just states "randomised". |

**Miller 2006**

| | |
|---|---|
| Methods | Method of randomisation: computer-generated sequence, stratified by admission accommodation. Sealed opaque envelopes, prepared remote from recruitment by pharmacy<br>Assessor blinding: not reported<br>Intention-to-treat analysis: carried out<br>Lost to follow-up: details given |
| Participants | Location: Orthopaedic wards of Flinders Medical Centre, Adelaide, Australia<br>Period of study: recruitment September 2000 to October 2002<br>43 hip fracture patients (out of a total of 51 with fall related lower limb fracture)*<br>Inclusion criteria: age 70 years or over, fall related lower limb fracture, resident in Southern Adelaide, malnourished (< $25^{th}$ percentile for mid-arm circumference for older Australians), written consent by patient or next of kin.<br>Exclusion criteria: unable to understand instructions for positioning of upper arm, could not full weight bear on side of injury > 7 days post admission, not independently mobile pre-fracture, medically unstable > 7 days post admission, cancer, chronic renal failure, unstable angina, diabetes.<br>Sex (of 51): 42 female, 9 male<br>Age (of 51): mean 83 years.<br>Fracture type: not given (aside from hip fracture = 43) |
| Interventions | Timing of intervention: from 7 days after fracture, given daily for 6 weeks<br>(a) Nutrition only intervention: Fortisip (Nutricia Australia Pty Ltd) oral protein and energy supplement (1.5 kcal/ml, 16% protein, 35% fat, 49% carbohydrate)to provide 45% of estimated energy intakes. ( Individually prescribed and delivered.)Four doses of equal volume given by nurses from drug trolley, continued after hospital discharge as twice per day or more. Once weekly visits on weeks 7 to 12.<br>(d) Attention control. Usual care and general nutrition and exercise advice. Twice weekly visits on weeks 1 to 6, once weekly on weeks 7 to 12.<br>Allocated: 23/20<br>Assessed: 23/20 (mortality) |
| Outcomes | Length of follow-up: 12 months<br>Main outcomes:<br>Mortality (for participants with hip fracture)<br>Length of hospital stay (acute, rehabilitation, total) (not available for participants with hip fracture)<br>Other outcomes:<br>Weight loss (not available for participants with hip fracture) |
| Notes | Trial population also included 49 other participants (43 with hip fracture), who were allocated to the two other intervention groups: exercise; and nutrition plus exercise. Data from these two groups are not included in this review.<br>Email to Professor Crotty 14 January 2009 asking for data for participants with hip fracture only; mortality data provided 20th February 2009. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | "The Pharmacy department maintained a computer generated allocation sequence in sealed opaque envelopes." |

**Neumann 2004**

| | |
|---|---|
| Methods | Method of randomisation: not stated, stratified by type of hip fracture<br>Assessor blinding: not reported<br>Intention-to-treat analysis: unclear<br>Lost to follow-up: details given |
| Participants | Location: 3 rehabilitation hospitals, USA<br>Period of study: unclear<br>46 participants<br>Inclusion criteria: within 3 weeks of surgical repair of hip fracture (intertrochanteric or femoral neck), expected to stay 1-3 weeks in rehabilitation, aged 60 years or over, BMI < 30 kg/m2, informed consent, able to be reached by phone after discharge<br>Exclusion criteria: fracture due to non-osteoporotic disease, e.g. pathological fracture; significant trauma to other organ systems or medical conditions significantly affecting outcome (severe hepatic dysfunction bilirubin > 3 mg/dL, severe renal dysfunction creatinine at least 3 mg/dL or dialysis, uncontrolled diabetes: 2 random blood glucose values > 200 mg/dL or > 140 mg/dL fasting)<br>Sex: 33 female, 13 male<br>Age: mean age 83 years<br>Fracture type: not given |
| Interventions | Timing of intervention: consecutive 28 day period at least two 8 oz cans/day<br>(a) Boost HP high protein liquid supplement (Mead Johnson, Evansville, Indiana, USA) providing per 8 oz can: 240 kcal, 15 g protein, 33 g carbohydrate, 6 g fat, 1110 IU vitamin A, 89 IU vitamin D, 6.7 IU vitamin E, 27 mcg vitamin K, 13.3 mg vitamin C, 89 mcg folic acid, 0.33 mg thiamin, 0.4 mg riboflavin, 0.47 mg vitamin B6, 1.33 mcg vitamin B12, 4.7 mg niacin, 56 mg choline, 67 mcg biotin, 2.3 mg pantothenic acid, 220 mg sodium, 490 mg potassium, 350 mg chloride, 240 mg calcium, 220 mg phosphorus, 90 mg magnesium, 33mg iodine, 0.67 mg manganese, 0.47 mg copper, 3.3 mg zinc, 4 mg iron, 15.8 mcg selenium, 27 mcg chromium, 16.9 mcg molybdenum<br>(b) Ensure liquid supplement (Ross Labs, Columbus, Ohio, USA) providing per 8 oz can: 250 kcal, 8.8 g protein, 40 g carbohydrate, 6.1 g fat, 1250 IU vitamin A, 100 IU vitamin D, 7.5 IU vitamin E, 20 mcg vitamin K, 30 mg vitamin C, 100 mcg folic acid, 0.38 mg thiamin, 0.43 mg riboflavin, 0.50 mg vitamin B6, 1.50 mcg vitamin B12, 5.0 mg niacin, 100 mg choline, 75 mcg biotin, 2.5 mg pantothenic acid, 200 mg sodium, 370 mg potassium, 310 mg chloride, 300 mg calcium, 300 mg phosphorus, 100 mg magnesium, 38 mcg iodine, 1.3 mg manganese, 0.50 mg copper, 3.8 mg zinc, 4.5 mg iron, 18 mcg selenium, 30 mcg chromium, 38 mcg molybdenum<br>Allocated: 22/24<br>Assessed: 18/20 for length of stay |
| Outcomes | Length of follow-up: 3 months<br>Main outcomes:<br>Mortality<br>Morbidity: complications (*nr), adverse events (*nr)<br>Length of rehabilitation hospital stay<br>Location for discharge<br>Postoperative functional status: mobility subscale of FIM instrument (Uniform Data System for Medical Rehabilitation)<br>Other outcomes:<br>Nutritional indicators measured in blood: albumin (subgroup data)<br>Other nutritional: days of supplement consumption |

**Neumann 2004** (*Continued*)

| | |
|---|---|
| Notes | Request for further details (deaths, denominators for length of stay, complications)sent 13/10/04. Details of deaths and denominators received 06/01/05 |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | No information on safeguards: "randomized, double-blind, parallel-group study" |

**Schürch 1998**

| | |
|---|---|
| Methods | Method of randomisation: states random number table and double-blind study, but unclear if those who assigned were blinded<br>Assessor blinding: unclear, no report of when code broken<br>Intention-to-treat analysis: unclear<br>Lost to follow-up: incomplete report of drop outs |
| Participants | Location: orthopaedic ward in hospital and recovery hospital, Geneva, Switzerland<br>Period of study: April 1992 to February 1994<br>82 participants<br>Inclusion criteria: hip fracture within 2 weeks attributable to osteoporosis (minor trauma), aged over 60 years, able to give written consent<br>Exclusion criteria: pathological fracture; fracture caused by severe trauma; history of contralateral hip fracture; severe mental impairment; active metabolic bone disease; renal failure (plasma creatinine equal to or greater than 200 mcmol/L); acute illness that could interfere with study protocol; severe malnutrition (serum albumin less than 15 g/L); on drugs known to alter bone metabolism, e.g. calcitonin, fluoride, sex hormones, corticosteroids, bisphosphonates; life expectancy less than 1 year<br>Sex: 74 female, 8 male<br>Age: mean 80.7 years<br>Fracture type: 31 cervical, 51 trochanteric |
| Interventions | Timing of intervention: mean randomisation time 6.5 (SD 1.9) days after fracture, supplemented 5 days a week for 6 months<br>(a) Oral protein supplement (1.05 MJ or 250 kcal, 20 g protein, 3.1 g fat, 35.7 g carbohydrate, 1000 IU vitamin A, 30 mcg vitamin K1, 20 mg vitamin C, 550 mg calcium, 91 mg magnesium, 429 mg phosphorus, 228 mg sodium) plus oral 200,000 IU vitamin D3 once at baseline during study<br>(b) Placebo without protein made isocaloric by addition of maltodextrins, plus oral 200,000 IU vitamin D3 once at baseline during study<br>Allocated: 41/41<br>Assessed: ?/? |
| Outcomes | Length of follow-up: 12 months<br>Main outcomes:<br>Mortality<br>Length of stay: orthopaedic ward, rehabilitation stay<br>Postoperative functional status: activities of daily living score<br>Putative side effects: drop outs due to nausea and diarrhoea |

**Schürch 1998** (*Continued*)

| | |
|---|---|
| | Other outcomes:<br>Anthropometric indices: body weight, whole body lean and fat mass, all (*nr)<br>Fractures : vertebral deformity<br>Bone mineral density: anteroposterior and lateral lumbar spine, femoral neck, trochanter, proximal femur, femoral shaft, whole body<br>Nutritional indicators measured in blood: albumin, prealbumin, insulin like growth factor I<br>Functional markers of nutritional status: biceps muscle strength, cell mediated immunity, hand grip (*nr)<br>Patient compliance: refusals |
| Notes | Composition of placebo unclear, denominators not clear. Request for further details sent 27/5/99, resent 7/2/00 |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | "Using a random number table, we assigned ..." Although "double-blind", it is unclear whether allocation was concealed. |

**Stableforth 1986**

| | |
|---|---|
| Methods | Method of randomisation: not stated<br>Assessor blinding: not reported<br>Intention-to-treat analysis: 3 excluded, intention-to-treat analysis not possible<br>Lost to follow-up: none |
| Participants | Location: hospital, Bristol, UK<br>Period of study: not given<br>61 participants<br>Inclusion criteria: people with hip fracture within 12 hours of fracture, women over 65 years<br>Exclusion criteria: none given<br>Sex: all female<br>Age: Mean 81.8 years, range 65-96 years<br>Fracture type: 23 trochanteric, 35 subcapital hip fractures (others not specified) |
| Interventions | Timing of intervention: started after surgery and 24 to 36 hours of crystalloid intravenous fluids. Intervention provided during waking hours for 10 days.<br>(a) Encouraged to drink flavoured, Carnation Instant Breakfast in 300 ml milk (1.34 MJ or 320 kcal, 18.5 g protein, 11 g fat, 40 g carbohydrate, vitamins and minerals) plus ward diet<br>(b) Ward diet alone<br>Allocated: ?/? 61 in all<br>Assessed: ?/? 61 in all |
| Outcomes | Length of follow-up: 4 weeks<br>Main outcomes:<br>Mortality: all causes<br>Morbidity and complications: anaesthetic, surgical infection, gastrointestinal, urinary<br>Other outcomes: |

**Stableforth 1986** (*Continued*)

| | |
|---|---|
| | Anthropometric indices: weight<br>Other nutritional: energy balance, nitrogen balance |
| Notes | Limited functional outcomes.<br>Request for further details, especially on longer term follow-up, sent 13/4/99, resent 7/2/00 |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | No information: "randomly selected group" |

**Sullivan 1998**

| | |
|---|---|
| Methods | Method of randomisation: sealed opaque envelopes opened sequentially<br>Assessor blinding: not reported<br>Intention-to-treat analysis: appears so<br>Lost to follow-up: none, all participants accounted for |
| Participants | Location: acute care facility, Little Rock, USA<br>Period of study: recruitment over 5 months, probably prior to 1998<br>18 participants<br>Inclusion criteria: aged over 64 years, acute hip fracture requiring surgery, admitted Monday to Friday<br>Exclusion criteria: unable to gain consent from patient or guardian, pathological fracture (cancer or non-osteoporotic), significant other system trauma, metastatic cancer, cirrhosis, contraindication to enteral feeding, organ failure<br>Sex: 1 female, 17 males<br>Age: mean 75.6 years<br>Fracture type: femoral neck or intertrochanteric |
| Interventions | Timing of intervention: small-bore nasogastric feeding tube placed in theatre or recovery room. Feeding started postoperatively, nightly from 19.00 hours, until volitional intake greater than 90% of predicted requirements for 3 consecutive days or participant discharged home.<br>(a) Nasogastric feeding via small bowel (or more proximally if low risk of aspiration): 1375 ml of polymeric enteral formula (Promote, Ross Laboratories, 85.8 g protein, 4.31 MJ or 1031 kcal non-nitrogenous energy, 71.5 g carbohydrate, 35.8 g fat, 88 mcg vitamin K, 77 mcg selenium, 110 mcg chromium, 165 mcg molybdenum, 165 mg carnitine, 165 mg taurine), given at 125 ml/h over 11 hours, plus standard care of 3 meals daily<br>(b) Standard care of 3 meals daily<br>Allocated: 8/10<br>Assessed: 8/7 for discharge statistics |
| Outcomes | Length of follow-up: 6 months<br>Main outcomes:<br>Mortality: in hospital and at 6 months<br>Morbidity and complications: postoperative life-threatening and minor complications<br>Length of stay: total acute care stay for survivors<br>Postoperative functional status: mini mental state exam score, Katz index of activities of daily living |

**Sullivan 1998** (*Continued*)

| | |
|---|---|
| | Care required after discharge: discharge to institution, total number of medications<br>Putative side effects of treatment: gastrointestinal<br>Other outcomes:<br>Nutritional indicators measured in blood: albumin, transferrin<br>Other nutritional: average daily volitional energy intake over first 7 postoperative days |
| Notes | Pilot study.<br>Request for further details (such as control group denominators)sent. Reply from trialist (10/2/00) gave further details of randomisation, place of care, complications, deaths, volitional food intake, nature of fracture, and content of supplement |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | "The actual randomization was prepared by the biostatistician.. using sealed envelopes. Security (lined) envelopes were used to assure that the assignment cannot be read without opening the envelope. After consent had been obtained and the baseline assessment was completed, the next envelope was opened to reveal the group assignment ..." Information from trialist. |

**Sullivan 2004**

| | |
|---|---|
| Methods | Method of randomisation: sealed opaque envelopes opened sequentially<br>Assessor blinding: not reported<br>Intention-to-treat analysis: appears so<br>Lost to follow-up: details given |
| Participants | Location: orthopaedic wards of University Hospital and Department of Veteran's Affairs Hospital, Little Rock, Arkansas, USA<br>Period of study: recruitment June 1996 to October 1997<br>57 participants<br>Inclusion criteria: over 64 years, acute femoral neck or intertrochanteric fracture treated surgically<br>Exclusion criteria: incapable of informed consent and no legal guardian, pathological fracture (cancer or not osteoporotic), significant trauma to other organ systems (e.g. motor vehicle accident), metastatic cancer, cirrhosis, enteral feeding contraindicated (e.g. short bowel), organ failure making intervention inappropriate<br>Sex: 18 female, 39 male<br>Age: mean age 79 years<br>Fracture type: 19 required endoprosthesis |
| Interventions | Timing of intervention: small bore feeding tube placed within 12 hours of surgery, confirmed by x-ray in place until deficit between requirements and oral intake < 480 kcal/day for at least 2 consecutive days or until discharged. Given nightly over 11 hours.<br>(a) Harris-Benedict equation with stress and activity factors used to predict requirements to make up |

| | |
|---|---|
| | deficit after food intake calculated - given as Promote (Ross Laboratories), 1000 kcal, 62.5 g protein, 130 g carbohydrate, 26 g fat per litre, if deficit > 480 kcal/day. If deficit 240-480 kcal/day, participant asked to drink supplement instead of tube feeding. Tube feeding begun at 50 ml/hour and increased by 25 ml/hour to maximum of 125 ml/hour. Given with standard care.<br>(b) Standard care<br>Allocated: 27/30<br>Assessed: 27/30 |
| Outcomes | Length of follow-up: 6 months<br>Main outcomes:<br>Mortality<br>Morbidity: postoperative and postoperative life-threatening complications, diarrhoea<br>Length of hospital stay<br>Level of care: discharge to an institution, medications at discharge<br>Postoperative functional status: Katz index of activities of daily living, Mini Mental State Exam score<br>Other outcomes:<br>Nutritional indicators measured in blood: albumin, pre-albumin<br>Other nutritional: energy intake |
| Notes | Request for further details on randomisation and tube feeding sent 15/03/06. Reply, received 14/04/06, gave further details of randomisation method. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | "The randomization process was prepared by the biostatistician, using a series of sealed envelopes. Security (lined) envelopes were used to assure that the assignment could not be read without opening the envelope. After consent had been obtained and the baseline assessment was completed, the next envelope in order was opened to reveal the group assignment. Each envelope contained a card. The card had the assignment for treatment or control pre-printed. Space was provided to enter the patient name and ID as well as the date, time and person responsible for randomization. The study nurse completed the card, photocopied it, and returned the original to the biostatistician as a check that the randomization process was progressing appropriately. Subjects were randomized to either treatment or control within blocks to assure that there were roughly equal numbers of subjects in each group at the end of the study. The block sizes were randomly varied to minimize the ability to deduce the assignment for a particular patient before opening the envelope." Reply from trialist. |

**Tidermark 2004**

| | |
|---|---|
| Methods | Method of randomisation: numbered opaque sealed envelopes, unclear if randomisation fully concealed since the envelopes prepared and opened by the same research nurse<br>Assessor blinding: not reported<br>Intention-to-treat analysis: appears so<br>Lost to follow-up: details given |
| Participants | Location: hospital(s) in Stockholm, Sweden<br>Period of study: before October 2002<br>40 participants<br>Inclusion criteria: age at least 70 years, BMI 24 kg/m2 or less, not institutionalised, absence of severe cognitive dysfunction, independent walking with or without walking aids<br>Exclusion criteria: fracture not suitable for internal fixation, displaced fracture older than 24 hours at time of arrival in emergency room, rheumatoid arthritis, radiographic osteoarthritis<br>Sex: all female<br>Age: mean age 84 years<br>Fracture type: 40 femoral neck (24 displaced) |
| Interventions | Timing of intervention: 6 months, unclear when started<br>(a) Fortimel protein rich liquid oral supplement, 20 g protein/200 ml, unclear if 200 or up to 400 ml/day<br>(b) Standard treatment<br>(c) Nandrolone decanoate (anabolic steroid) 25 mg intramuscular injection/3 weeks and Fortimel as in (a): group not included in review<br>Allocated: 20/20<br>Assessed: 20/20 for mortality |
| Outcomes | Length of follow-up: 12 months<br>Main outcomes:<br>Mortality<br>Morbidity and complications: deep infection, urinary tract infection, fracture healing complication<br>Length of hospital stay<br>Activities of daily living: Katz score, mobility<br>Quality of life: EuroQol<br>Fracture healing<br>Adverse events<br>Other outcomes:<br>Changes in anthropometric indices: weight, BMI, lean body mass, fat mass<br>Changes in nutritional indicators measured in blood: albumin, C-reactive protein, (IGF-I) insulin-like growth factor-I, (IGFBP-I) IGF-binding protein I<br>Bone mineral density<br>Functional markers of nutritional status: hand grip strength<br>Patient compliance |
| Notes | Request for further details (complications)sent. Reply from trialist (14/10/04) gave further details of infections. Request for further details (randomisation)sent. Reply from trialist (10/11/04) gave full details of randomisation process. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|

**Tidermark 2004** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment? | Unclear | "Patients were randomised, using opaque sealed envelopes". (Also numbered.)However, the envelopes were prepared and opened by the same research nurse, involved in the trial. |

**Tkatch 1992**

| | |
|---|---|
| Methods | Method of randomisation: not stated<br>Assessor blinding: not reported<br>Intention-to-treat analysis: not carried out, at least 6 participants excluded after randomisation<br>Lost to follow-up: none, all participants accounted for |
| Participants | Location: orthopaedic ward, hospital and recovery hospital, Geneva, Switzerland<br>Period of study: 17 consecutive weeks, probably prior to 1992<br>72 participants<br>Inclusion criteria: subcapital or trochanteric fracture of the proximal femur following moderate trauma, aged over 60 years<br>Exclusion criteria: fracture resulting from violent injury, primary or metastatic bone tumour; renal osteodystrophy; hepatic insufficiency; endocrine disorders affecting skeletal metabolism; chronic alcoholism; advanced dementia; contralateral reunited hip fracture; refusal to participate; corticosteroid, fluoride, phenytoin treatment; Paget's disease; non residence in Geneva, left orthopaedic unit prematurely after conservative treatment for subcapital fracture<br>Sex: 54 female, 8 male, of 62<br>Age: mean age 82 years<br>Fracture type: 32 subcapital, 30 trochanteric |
| Interventions | Timing of intervention: started on admission to orthopaedic clinic, continued in recovery hospital. Given once daily at 20.00 hours<br>(a) Protein supplement (20.4 g protein from milk) in 250 ml of oral supplement (5.8 g fat, 29.5 g carbohydrate, 525 mg calcium, 70 mg magnesium, 270 mg phosphorus, 25 IU vitamin D3, 750 IU vitamin A)<br>(b) 250 ml of oral supplement alone<br>Allocated: ?/?<br>Assessed: 33/29 |
| Outcomes | Length of follow-up: 7 months<br>Main outcomes:<br>Mortality<br>Morbidity and complications: complications (bedsore, anaemia, cardiac failure, infection, digestive disturbance, other), favourable clinical course (excludes death, major complication, or two or more minor complications)<br>Length of stay: orthopaedic ward and recovery hospital<br>Care required after discharge: still in hospital at 7 months, returned home at 7 months<br>Other outcomes:<br>Fractures: hip and other fractures<br>Bone mineral density: femoral neck, femoral shaft, lumbar spine<br>Nutritional indicators measured in blood: albumin (*nr)<br>Patient compliance: non compliance taking supplement, controls taking protein supplement |

**Tkatch 1992** (*Continued*)

| | |
|---|---|
| Notes | Post-randomisation exclusions: 3 in protein intervention group excluded for non-compliance, 3 controls excluded (2 took protein supplements, one severe diarrhoea), 4 of unspecified group left orthopaedic unit prematurely. Numbers of complications unclear. Request for further details (exclusions, complications) sent 24/5/99, resent 7/2/00 |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | No information: just "randomized into two groups". |

BMI: body mass index
NHS: UK National Health Service
mosmol/L: milliosmoles/L, a measure of osmolality
*nr: no results
SD: standard deviation

## Characteristics of excluded studies *[ordered by study ID]*

| | |
|---|---|
| Ashworth 2006 | Pilot study for randomised controlled trial of snacks versus oral nutritional supplements. Trial stopped early as only four out of 95 patients were eligible for recruitment. No relevant outcomes. |
| Bachrach 2000 | Randomised controlled trial of total hip arthroplasty versus osteosynthesis for hip fracture, but not of nutritional supplementation. The second half of each surgical treatment group received nutritional supplementation; thus, the supplementation and control groups were also not concurrent. |
| Bachrach 2001 | Study of protein and energy supplementation after hip fracture. Not a randomised controlled trial: non concurrent study groups. |
| Beringer 1986 | Randomised controlled trial. Comparison between 880 mg calcium and 80 mg calcium with 5 mg of anabolic steroid stanozolol. Not both nutrition interventions, and required outcomes not evaluated. |
| Boudville 2002 | Short-term study the effect on the appetite of 250 kcal supplement of people with hip or pelvic fracture. Unclear if randomised controlled trial. No relevant outcomes. |
| Bradley 1995 | Not a randomised controlled trial: nursing education programme targeting specific problems including nutritional deficits. |
| Brocker 1994 | The 194 ambulatory elderly participants in the trial are unlikely to include people with hip fracture. No response from author. |

(*Continued*)

| | |
|---|---|
| Carlsson 2005 | Randomised controlled trial of protein-rich liquid supplement versus supplement with nandrolone decanoate injections. Not in scope of review. |
| Crossley 1977 | Unable to contact author. Contacted project supervisor, thesis no longer available. |
| Gegerle 1986 | Randomised controlled trial of 250 ml oral supplement providing 20 g protein, 254 kcal, minerals and vitamins. Study reports only effects of supplement on intake of intervention group, compared to control group. No other outcomes provided. French paper - checked by French translator. |
| Giaccaglia 1986 | Not a randomised controlled trial. Italian paper - checked by Italian translator. |
| Goldsmith 1967 | Not people with hip fracture. |
| Groth 1988 | Not people with hip fracture nor a randomised controlled trial. |
| Harju 1989 | Comparison of 0.25 mcg 1-alpha-hydroxyvitamin D3, 100 IU calcitonin and placebo in women after femoral neck fracture. No outcomes of interest given, possibly not a randomised controlled trial. |
| Harwood 2004 | Randomised controlled trial, involving 150 women after hip fracture, comparing single injection of 300,000 IU vitamin D2, injected vitamin D2 and 1000 mg/d oral calcium, 800 IU/d oral vitamin D3 and 1000 mg/d calcium, or no treatment. Secondary prevention trial. |
| Hedström 2002 | Randomised controlled trial, involving 63 women after hip fracture, comparing nandrolone decanoate (25 mg intramuscularly every three weeks), 0.25 mcg 1-alpha-hydroxyvitamin D3 daily and 500 mg calcium daily versus 500 mg calcium daily. Thus this evaluated anabolic steroid and vitamin D together. |
| Hommel 2007 | Quasi-experimental before and after study of best practices for people with hip fracture, with nutritional drink as one component of the intervention (clinical pathway). |
| Kacmaz 2007 | Non-randomised comparison of bran supplements and nursing intervention versus usual nursing care in post-operative orthopaedic patients, mean age 69 years. Unclear if any patient had hip fracture. |
| Kuzdenbaeva 1981 | Comparative study, not explicitly randomised. Mixed group of hip fracture and femoral shaft fracture participants aged 17 to 67 years; thus majority of hip fracture participants were not over 65 years. Russian paper - checked by Russian translator. |
| Larsson 1990 | Randomised trial of older people, of whom 89 had fractures, newly admitted to long-term medical care. No response from lead author to requests for separate results for participants with hip fracture. |
| Lauque 2000 | Randomised controlled trial of protein and energy supplementation in nursing homes; not specifically directed at people after hip fracture. |
| Lawson 2003 | Not a randomised controlled trial. Mixed group of orthopaedic patients. |
| Moller-Madsen 1988 | No usable results published in conference abstract reporting trial of oral supplements for 25 people with hip fracture. No response from authors. |

(*Continued*)

| | |
|---|---|
| Nusbickel 1989 | No response from author. No information in the two conference abstracts reports of the trial of how many people with hip fracture were included, nor their results. |
| Oloffson 2007 | Randomised trial of a multidisciplinary intervention programme for people after hip fracture. The nutritional intervention was only one component of the complex intervention. |
| Pedersen 1999 | Intervention and control groups were not concurrent, nor randomised. The trial investigated the effects of active involvement of orthopaedic patients in their own dietary care; thus the intervention was not direct nutritional supplementation but rather a means of enhancing update by patients. Mixed patient population with hip fracture, or undergoing knee or hip arthroplasty. |
| Ravetz 1959 | Two hip fracture patients only. Unlikely to be a randomised controlled trial. |
| Shaikhiev 1984 | Comparative study, not explicitly randomised. Mixed group of hip fracture and femoral shaft fracture participants aged 17 to 65 years; thus majority of hip fracture participants were not over 65 years. Russian paper - checked by Russian translator. |
| Stumm 2001 | Randomised controlled trial testing the addition of pear juice or high fibre supplement to normal diet versus normal diet alone in a mixed group of orthopaedic patients admitted for elective surgery or after traumatic fracture. Aimed at the management of constipation and not for improvement of nutritional status; no relevant outcomes. |
| Tassler 1981 | Not randomised controlled trial. German paper. |
| Taylor 1974 | Quasi-randomised placebo-controlled trial of vitamin C: patients recruited with pressure sores, not because of hip fracture, although nine out of 20 participants had hip fracture. |
| Thomas 2008 | Randomised controlled trial of resistance training and nutrition therapy combined versus attention control. Unable to assess effect of nutrition separately. |
| Volkert 1996 | Randomised controlled trial involving a mixed group of medical, general surgical and orthopaedic patients aged over 75 years. Author indicates that only a few participants had hip fractures. |
| Williams 1989 | This trial appears to form part of one of three consecutive studies published in the PhD thesis of Driver (Driver LT. Evaluation of supplemental nutrition in elderly orthopaedic patients [PhD thesis]. Surrey (UK): Univ. of Surrey, 1994). All three studies evaluated nutritional supplementation in a combined group of hip fracture and elective hip replacement patients. There were major defects in the randomisation process, as well as numerical discrepancies, which suggest intention to treat problems. We have been unable to contact Driver to obtain clarification of the status of the three studies, the trial populations and further specific information on the participants with hip fracture. For the purposes of this review, the three studies have been represented as one trial. |
| Wong 2004 | Randomised controlled trial of dietetic counselling versus usual care in a mixed patient group with osteoporotic fractures (forearm, vertebral, hip). Limited outcomes only (energy, protein and calcium intake, weight and BMI) |
| Zauber 1992 | Randomised controlled trial. Mixed group of elective hip replacement and hip fracture patients. Some participants were excluded from the analysis. Limited outcomes only (haemoglobin and reticulocyte count). |

## Characteristics of studies awaiting assessment *[ordered by study ID]*

**Gerstorfer 2008**

| | |
|---|---|
| Methods | Controlled trial: "randomly divided" |
| Participants | 46 women with hip fracture, mean age 83 years |
| Interventions | (a) Nutritional therapeutic regime (protocols, protein enriched food, oral and/or parenteral supplementation).<br>(b) Usual care. |
| Outcomes | Nutritional biochemistry |
| Notes | Email to Dr Elmadfa on 3rd October 2008 asking for further details |

**Stratton 2006**

| | |
|---|---|
| Methods | Randomised controlled trial |
| Participants | 50 men and women with fractured neck of femur, at risk of malnutrition |
| Interventions | (a) Liquid multinutrient oral nutritional support.<br>(b) Food snacks. |
| Outcomes | Compliance, patient satisfaction |
| Notes | Email to Dr Stratton on 3rd October 2008 asking for further details |

## Characteristics of ongoing studies *[ordered by study ID]*

**Cameron**

| | |
|---|---|
| Trial name or title | Effectiveness of oral supplementation for older women with hip and other fractures (EONS) |
| Methods | Randomised controlled trial. |
| Participants | 43 older women with hip or other fractures. |
| Interventions | (a) Oral nutritional supplementation: 235 ml (1.5 kcal/ml) daily for 40 days.<br>(b) Usual care. |
| Outcomes | Follow-up: 1 and 4 months post fracture.<br>Outcomes: ADL function, nutritional status and medical complications |
| Starting date | Started April 2000. Recruitment completed and follow-up completed. |

**Cameron** (*Continued*)

| | |
|---|---|
| Contact information | Prof Ian Cameron<br>Rehabilitation Studies Unit<br>University of Sydney<br>PO Box 6<br>Ryde<br>New South Wales AUSTRALIA<br>NSW 1680<br>Telephone: +61 2 9808 9236<br>Facsimile: +61 2 9809 9037<br>E-mail:<br>ianc@mail.usyd.edu.au |
| Notes | Randomised using sealed opaque envelopes with sequence generated from random number table. Updated information received from Ian Cameron in July 2003; when 43 trial participants had completed follow-up. Study completion confirmed by Ian Cameron in October 2004.<br>Analysis ongoing confirmed by Ian Cameron October 2008. |

**Dagnelie**

| | |
|---|---|
| Trial name or title | Effectiveness and cost-effectiveness of nutritional screening and intervention in elderly subjects after hip fracture |
| Methods | Randomised controlled trial |
| Participants | People aged 55 years or older with hip fracture from three centres in The Netherlands |
| Interventions | (a) Protein and energy enriched oral nutritional supplements and regular dietetic counselling during hospitalisation and after discharge at participants' homes for 3 months.<br>(b) Usual nurse and dietetic care. |
| Outcomes | Follow-up: 3 and 6 months after trial inclusion<br>Outcomes: total length of stay in hospital and rehabilitation, functional status, quality of life, costs, informal care, complications, nutritional status |
| Starting date | August 2007, due to complete August 2009 for primary outcome measure |
| Contact information | Dr PC Dagnelie and Dr PLM Reijven<br>Maastricht University<br>The Netherlands<br>Contacts:caroline.wyers@epid.unimaas.nl; p.reijven@epid.unimaas.nl |
| Notes | |

**Houdijk**

| | |
|---|---|
| Trial name or title | The effect of taurine on morbidity and mortality in the elderly hip fracture patient |
| Methods | Randomised controlled double-blind trial |
| Participants | Aged over 75 years, surgery for hip fracture, both genders |
| Interventions | (a) 3 g taurine / day or 6 g taurine / day<br>(b) placebo |
| Outcomes | Follow-up: 1 year<br>Outcome: morbidity and mortality |
| Starting date | July 2007, expected completion July 2010 |
| Contact information | Dr Alexander PJ Houdijk<br>Medical Center Alkmaar<br>Alkmaar<br>Noord-Holland<br>1800 AM<br>The Netherlands<br>Telephone: +31 72 5484444 ext: 5383<br>E-mail: a.p.j.houdijk@mca.nl |
| Notes | |

**Miller**

| | |
|---|---|
| Trial name or title | Does a high dose fish oil intervention improve outcomes in older adults recovering from hip fracture? |
| Methods | Randomised controlled double-blind trial |
| Participants | 150 men and women, aged 65 years or over, after surgical fixation of femoral fracture, history of recent unexplained weight loss and at risk of further weight loss and current poor appetite, elevated C reactive protein (6 mg/L or more), serum albumin < 35 g/L, raised energy expenditure. |
| Interventions | (a) 15 ml/day liquid fish oil orally (4.9 g eicosapentaenoic acid and 3.4 g docosahexaenoic acid) and individualised nutrition therapy.<br>(b) Low-dose plant and fish oil supplement 15 ml/day (0.49 g eicosapentaenoic acid and 0.39 g docosahexaenoic acid) and individualised nutrition therapy.<br>Both for 12 weeks. |
| Outcomes | Follow-up: 6 and 12 weeks<br>Outcome: health related quality of life, physical function, nutritional status, resting energy expenditure, inflammatory markers. |
| Starting date | February 2010 |

**Miller** (*Continued*)

| | |
|---|---|
| Contact information | Dr Michelle Miller<br>Department of Nutrition and Dietetics<br>Flinders University<br>GPO Box 2100<br>Adelaide SA 5001<br>Australia<br>E-Mail: michelle.miller@flinders.edu.au |
| Notes | |

ADL: activities of daily living

## DATA AND ANALYSES

### Comparison 1. Multinutrient supplement (oral, nasogastric, intravenous) versus control

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mortality by end of study | 14 | 887 | Risk Ratio (M-H, Fixed, 99% CI) | 0.77 [0.51, 1.15] |
| 1.1 Oral supplements | 9 | 470 | Risk Ratio (M-H, Fixed, 99% CI) | 0.76 [0.42, 1.37] |
| 1.2 Nasogastric tube feeding | 3 | 280 | Risk Ratio (M-H, Fixed, 99% CI) | 0.99 [0.50, 1.97] |
| 1.3 Nasogastric tube feeding and oral supplements | 1 | 57 | Risk Ratio (M-H, Fixed, 99% CI) | 0.74 [0.23, 2.35] |
| 1.4 Intravenous feeding and oral supplements | 1 | 80 | Risk Ratio (M-H, Fixed, 99% CI) | 0.11 [0.01, 2.00] |
| 2 Patients with complications at end of study | 9 | 454 | Risk Ratio (M-H, Fixed, 99% CI) | 0.71 [0.57, 0.89] |
| 2.1 Oral supplements | 6 | 299 | Risk Ratio (M-H, Fixed, 99% CI) | 0.81 [0.58, 1.13] |
| 2.2 Nasogastric tube feeding | 1 | 18 | Risk Ratio (M-H, Fixed, 99% CI) | 1.09 [0.73, 1.64] |
| 2.3 Nasogastric tube feeding and oral supplements | 1 | 57 | Risk Ratio (M-H, Fixed, 99% CI) | 1.11 [0.75, 1.65] |
| 2.4 Intravenous feeding and oral supplements | 1 | 80 | Risk Ratio (M-H, Fixed, 99% CI) | 0.21 [0.10, 0.46] |
| 3 Patients with complications at end of study: random-effects model | 9 | 454 | Risk Ratio (M-H, Random, 99% CI) | 0.73 [0.47, 1.12] |
| 3.1 Oral supplements | 6 | 299 | Risk Ratio (M-H, Random, 99% CI) | 0.86 [0.62, 1.20] |
| 3.2 Nasogastric tube feeding | 1 | 18 | Risk Ratio (M-H, Random, 99% CI) | 1.09 [0.73, 1.64] |
| 3.3 Nasogastric tube feeding and oral supplements | 1 | 57 | Risk Ratio (M-H, Random, 99% CI) | 1.11 [0.75, 1.65] |
| 3.4 Intravenous feeding and oral supplements | 1 | 80 | Risk Ratio (M-H, Random, 99% CI) | 0.21 [0.10, 0.46] |
| 4 Unfavourable outcome (death or complications) at end of study | 4 | 229 | Risk Ratio (M-H, Fixed, 99% CI) | 0.76 [0.55, 1.04] |
| 4.1 Oral supplements | 4 | 229 | Risk Ratio (M-H, Fixed, 99% CI) | 0.76 [0.55, 1.04] |
| 4.2 Nasogastric tube feeding | 0 | 0 | Risk Ratio (M-H, Fixed, 99% CI) | Not estimable |
| 4.3 Nasogastric tube feeding and oral supplements | 0 | 0 | Risk Ratio (M-H, Fixed, 99% CI) | Not estimable |
| 4.4 Intravenous feeding and oral supplements | 0 | 0 | Risk Ratio (M-H, Fixed, 99% CI) | Not estimable |
| 5 Unfavourable outcome (death or complications) at end of study: random-effects model | 4 | 229 | Risk Ratio (M-H, Random, 99% CI) | 0.71 [0.41, 1.22] |
| 5.1 Oral supplements | 4 | 229 | Risk Ratio (M-H, Random, 99% CI) | 0.71 [0.41, 1.22] |
| 5.2 Nasogastric tube feeding | 0 | 0 | Risk Ratio (M-H, Random, 99% CI) | Not estimable |
| 5.3 Nasogastric tube feeding and oral supplements | 0 | 0 | Risk Ratio (M-H, Random, 99% CI) | Not estimable |
| 5.4 Intravenous feeding and oral supplements | 0 | 0 | Risk Ratio (M-H, Random, 99% CI) | Not estimable |

| | | | | |
|---|---|---|---|---|
| 6 Unfavourable outcome (death or complications) - oral supplements extra analyses | 4 | | Risk Ratio (M-H, Fixed, 99% CI) | Subtotals only |
| 6.1 Oral supplements: worst case scenario | 4 | 238 | Risk Ratio (M-H, Fixed, 99% CI) | 0.85 [0.62, 1.15] |
| 6.2 Oral supplements: Hankins 1996 acute hospital data | 1 | 31 | Risk Ratio (M-H, Fixed, 99% CI) | 0.96 [0.71, 1.31] |
| 6.3 Oral supplements: Hankins 1996 post discharge | 1 | 31 | Risk Ratio (M-H, Fixed, 99% CI) | 1.10 [0.50, 2.41] |

**Comparison 2. Multinutrient supplements (oral, nasogastric routes, intravenous) versus control (split by nutritional status)**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mortality by end of study | 14 | 887 | Risk Ratio (M-H, Fixed, 95% CI) | 0.77 [0.51, 1.15] |
| 1.1 Malnourished targeted | 4 | 206 | Risk Ratio (M-H, Fixed, 95% CI) | 0.52 [0.25, 1.07] |
| 1.2 Malnourished not targeted | 10 | 681 | Risk Ratio (M-H, Fixed, 95% CI) | 0.92 [0.56, 1.53] |
| 2 Patients with complications at end of study | 9 | 454 | Risk Ratio (M-H, Fixed, 99% CI) | 0.71 [0.57, 0.89] |
| 2.1 Malnourished targeted | 1 | 29 | Risk Ratio (M-H, Fixed, 99% CI) | 0.59 [0.23, 1.49] |
| 2.2 Malnourished not targeted | 8 | 425 | Risk Ratio (M-H, Fixed, 99% CI) | 0.72 [0.57, 0.91] |
| 3 Unfavourable outcome (death or complications) at end of study | 4 | 229 | Risk Ratio (M-H, Fixed, 99% CI) | 0.76 [0.55, 1.04] |
| 3.1 Malnourished targeted | 1 | 29 | Risk Ratio (M-H, Fixed, 99% CI) | 0.47 [0.17, 1.31] |
| 3.2 Malnourished not targeted | 3 | 200 | Risk Ratio (M-H, Fixed, 99% CI) | 0.81 [0.58, 1.12] |

**Comparison 3. Multinutrient supplements (oral, nasogastric routes, intravenous) versus control (by allocation concealment)**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mortality by end of study (concealed? = yes; unclear; no) | 14 | 887 | Risk Ratio (M-H, Fixed, 99% CI) | 0.77 [0.51, 1.15] |
| 1.1 Allocation concealed | 5 | 239 | Risk Ratio (M-H, Fixed, 99% CI) | 0.39 [0.18, 0.85] |
| 1.2 Unclear if allocation concealed | 6 | 407 | Risk Ratio (M-H, Fixed, 99% CI) | 1.22 [0.65, 2.28] |
| 1.3 Allocation not concealed (quasi-randomised) | 3 | 241 | Risk Ratio (M-H, Fixed, 99% CI) | 0.78 [0.34, 1.79] |

**Comparison 4. High protein containing supplements versus low protein or non-protein containing supplements**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mortality by end of study | 4 | 361 | Risk Ratio (M-H, Fixed, 99% CI) | 1.42 [0.85, 2.37] |
| 1.1 Protein containing supplement v non-protein containing supplement | 3 | 315 | Risk Ratio (M-H, Fixed, 99% CI) | 1.38 [0.82, 2.34] |
| 1.2 High protein containing supplement v low protein containing supplement | 1 | 46 | Risk Ratio (M-H, Fixed, 99% CI) | 2.18 [0.21, 22.42] |
| 2 Unfavourable outcome (death or complications) at end of study | 2 | 223 | Risk Ratio (M-H, Fixed, 99% CI) | 0.78 [0.65, 0.95] |
| 2.1 Protein containing supplement v non-protein containing supplement | 2 | 223 | Risk Ratio (M-H, Fixed, 99% CI) | 0.78 [0.65, 0.95] |

**Comparison 5. Thiamin (vitamin B1) and water soluble vitamins versus control**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mortality by end of study | 1 | | Risk Ratio (M-H, Fixed, 99% CI) | Totals not selected |
| 2 Patients with complications at end of study | 1 | | Risk Ratio (M-H, Fixed, 99% CI) | Totals not selected |

**Comparison 6. Vitamin D versus control**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Patients with complications at end of study | 1 | | Risk Ratio (M-H, Fixed, 99% CI) | Totals not selected |

## Comparison 7. Dietetic assistants versus usual care

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mortality by end of study | 1 | | Risk Ratio (M-H, Fixed, 99% CI) | Totals not selected |
| 2 Patients with complications at end of study | 1 | | Risk Ratio (M-H, Fixed, 99% CI) | Totals not selected |

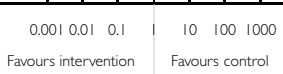
### Analysis 1.1. Comparison 1 Multinutrient supplement (oral, nasogastric, intravenous) versus control, Outcome 1 Mortality by end of study.

Review: Nutritional supplementation for hip fracture aftercare in older people

Comparison: 1 Multinutrient supplement (oral, nasogastric, intravenous) versus control

Outcome: 1 Mortality by end of study

| Study or subgroup | Intervention n/N | Control n/N | Risk Ratio M-H,Fixed,99% CI | Risk Ratio M-H,Fixed,99% CI |
|---|---|---|---|---|
| 1 Oral supplements | | | | |
| Botella-Carretero 2008 | 0/60 | 0/30 | | 0.0 [ 0.0, 0.0 ] |
| Brown 1992 | 0/5 | 0/5 | | 0.0 [ 0.0, 0.0 ] |
| Bruce 2003 | 2/50 | 2/59 | | 1.18 [ 0.09, 14.78 ] |
| Delmi 1990 | 6/27 | 10/32 | | 0.71 [ 0.23, 2.24 ] |
| Hankins 1996 | 2/17 | 4/14 | | 0.41 [ 0.05, 3.13 ] |
| Madigan 1994 | 4/18 | 0/12 | | 6.16 [ 0.15, 255.68 ] |
| Miller 2006 | 1/23 | 4/20 | | 0.22 [ 0.01, 3.47 ] |
| Stableforth 1986 | 0/24 | 0/34 | | 0.0 [ 0.0, 0.0 ] |
| Tidermark 2004 | 1/20 | 1/20 | | 1.00 [ 0.03, 34.83 ] |
| **Subtotal (95% CI)** | **244** | **226** | | **0.76 [ 0.42, 1.37 ]** |
| Total events: 16 (Intervention), 21 (Control) | | | | |
| Heterogeneity: $Chi^2$ = 4.31, df = 5 (P = 0.51); $I^2$ =0.0% | | | | |
| Test for overall effect: Z = 0.92 (P = 0.36) | | | | |
| 2 Nasogastric tube feeding | | | | |
| Bastow 1983 | 7/64 | 9/58 | | 0.70 [ 0.21, 2.37 ] |
| Hartgrink 1998 | 7/70 | 0/70 | | 15.00 [ 0.36, 629.78 ] |
| Sullivan 1998 | 0/8 | 5/10 | | 0.11 [ 0.00, 4.17 ] |
| **Subtotal (95% CI)** | **142** | **138** | | **0.99 [ 0.50, 1.97 ]** |

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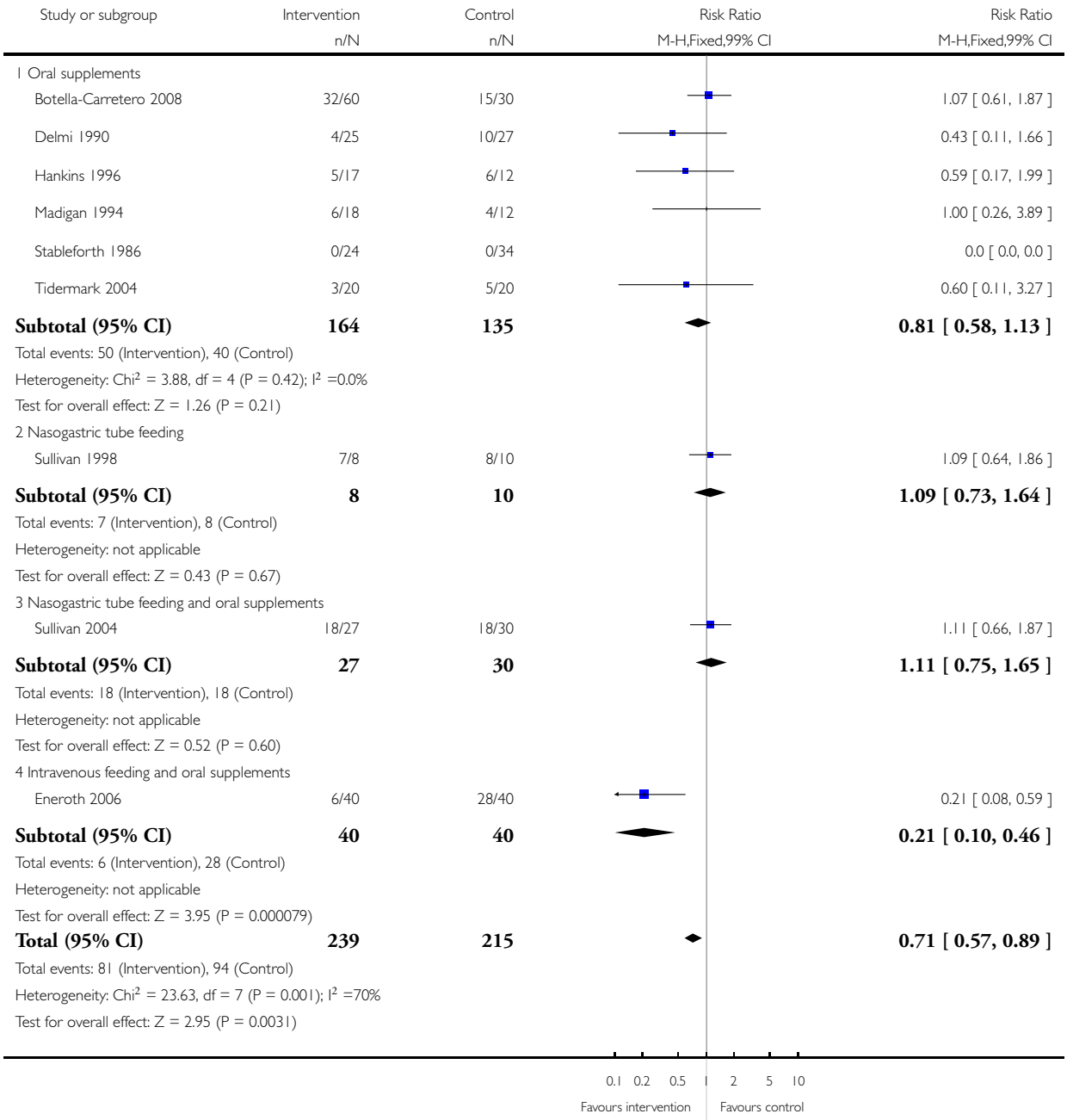
| Study or subgroup | Intervention n/N | Control n/N | Risk Ratio M-H,Fixed,99% CI | Risk Ratio M-H,Fixed,99% CI |
|---|---|---|---|---|
| Total events: 14 (Intervention), 14 (Control) | | | | |
| Heterogeneity: Chi² = 6.44, df = 2 (P = 0.04); I² =69% | | | | |
| Test for overall effect: Z = 0.04 (P = 0.97) | | | | |
| 3 Nasogastric tube feeding and oral supplements | | | | |
| Sullivan 2004 | 4/27 | 6/30 | | 0.74 [ 0.16, 3.37 ] |
| **Subtotal (95% CI)** | **27** | **30** | | **0.74 [ 0.23, 2.35 ]** |
| Total events: 4 (Intervention), 6 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 0.51 (P = 0.61) | | | | |
| 4 Intravenous feeding and oral supplements | | | | |
| Eneroth 2006 | 0/40 | 4/40 | | 0.11 [ 0.00, 4.95 ] |
| **Subtotal (95% CI)** | **40** | **40** | | **0.11 [ 0.01, 2.00 ]** |
| Total events: 0 (Intervention), 4 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 1.49 (P = 0.14) | | | | |
| **Total (95% CI)** | **453** | **434** | | **0.77 [ 0.51, 1.15 ]** |
| Total events: 34 (Intervention), 45 (Control) | | | | |
| Heterogeneity: Chi² = 12.16, df = 10 (P = 0.27); I² =18% | | | | |
| Test for overall effect: Z = 1.27 (P = 0.20) | | | | |

## Analysis 1.2. Comparison 1 Multinutrient supplement (oral, nasogastric, intravenous) versus control, Outcome 2 Patients with complications at end of study.

Review: Nutritional supplementation for hip fracture aftercare in older people

Comparison: 1 Multinutrient supplement (oral, nasogastric, intravenous) versus control

Outcome: 2 Patients with complications at end of study

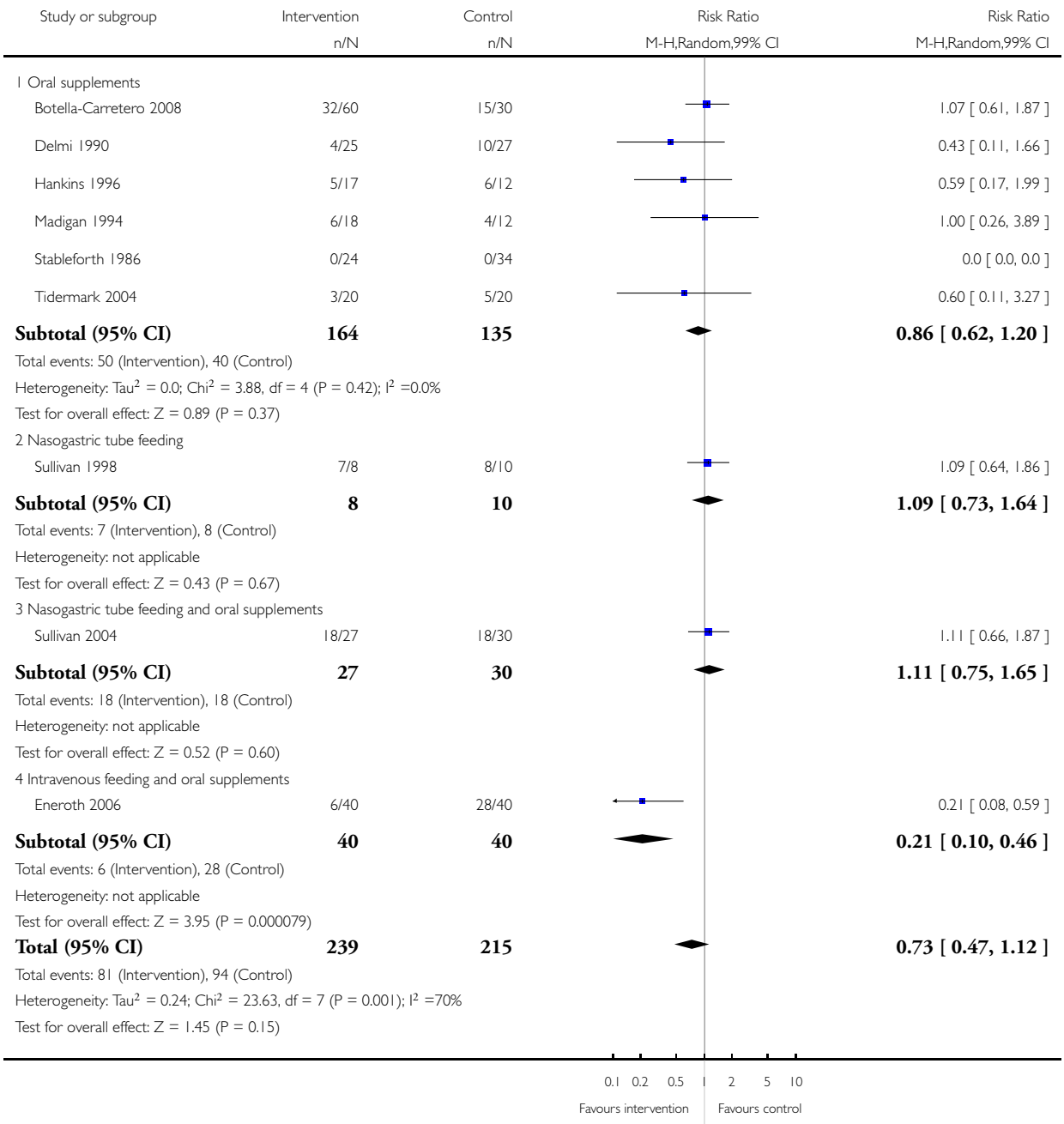


## Analysis 1.3. Comparison 1 Multinutrient supplement (oral, nasogastric, intravenous) versus control, Outcome 3 Patients with complications at end of study: random-effects model.

Review: Nutritional supplementation for hip fracture aftercare in older people

Comparison: 1 Multinutrient supplement (oral, nasogastric, intravenous) versus control

Outcome: 3 Patients with complications at end of study: random-effects model

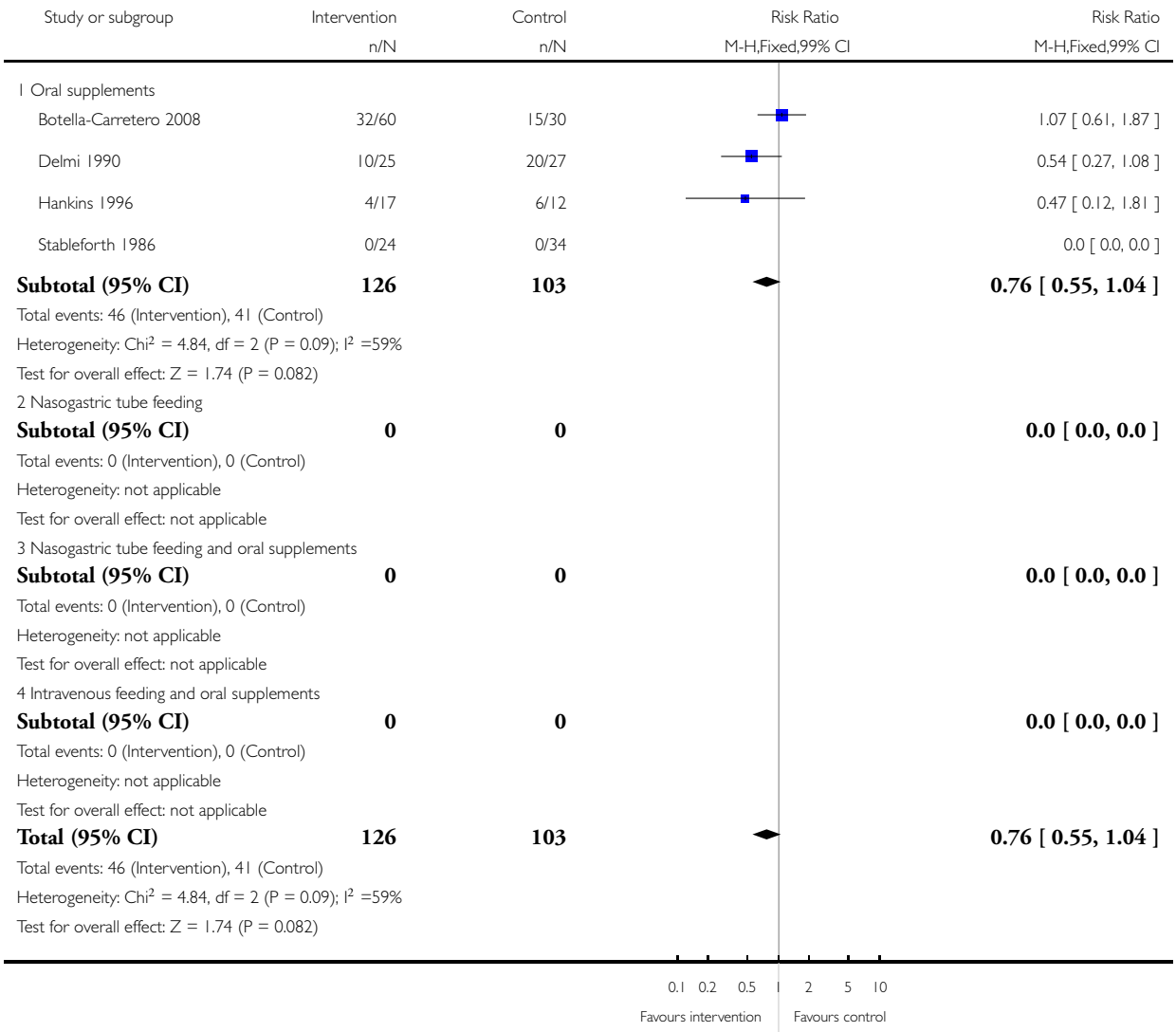


## Analysis 1.4. Comparison 1 Multinutrient supplement (oral, nasogastric, intravenous) versus control, Outcome 4 Unfavourable outcome (death or complications) at end of study.

Review: Nutritional supplementation for hip fracture aftercare in older people

Comparison: 1 Multinutrient supplement (oral, nasogastric, intravenous) versus control

Outcome: 4 Unfavourable outcome (death or complications) at end of study

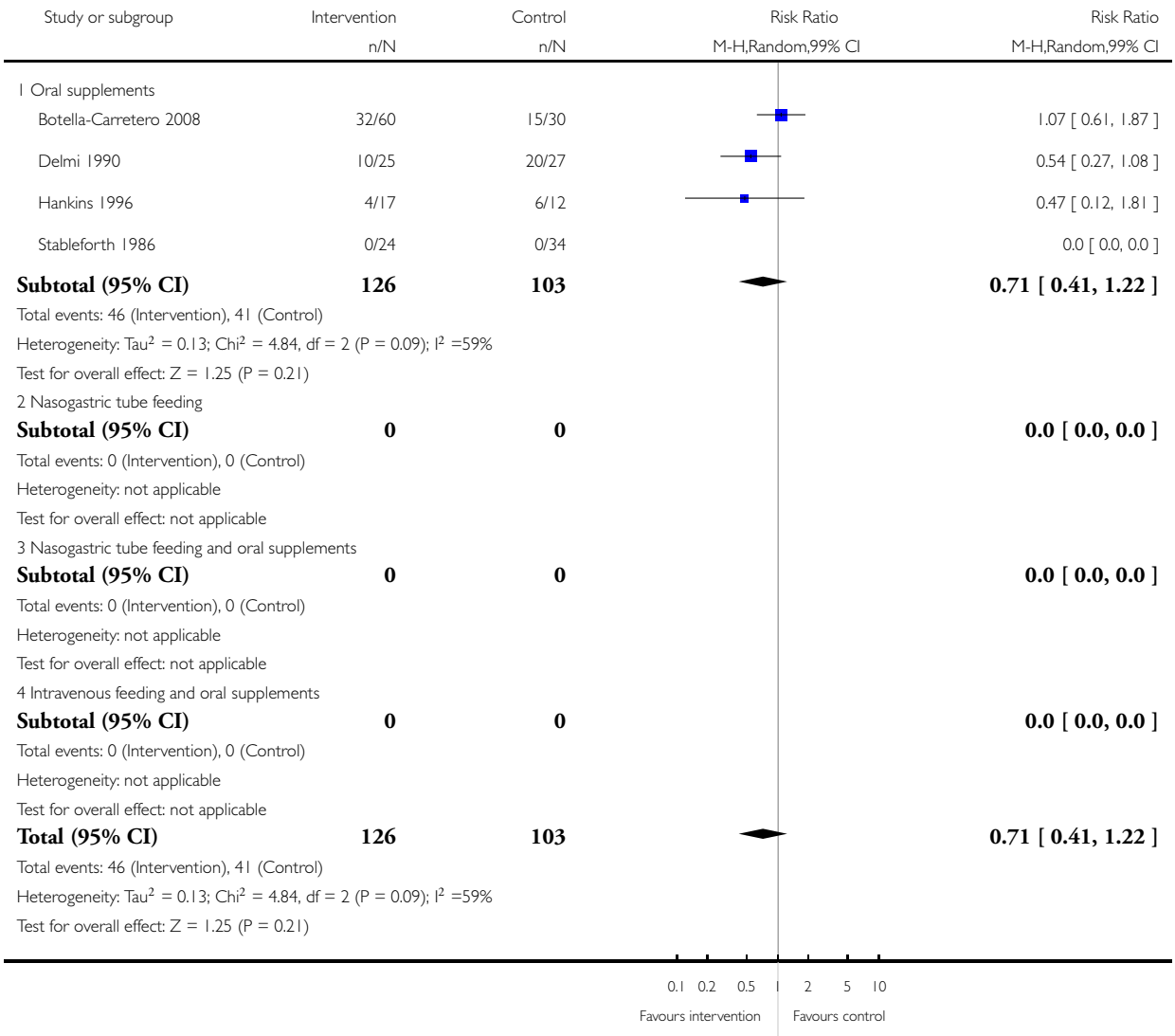


### Analysis 1.5. Comparison 1 Multinutrient supplement (oral, nasogastric, intravenous) versus control, Outcome 5 Unfavourable outcome (death or complications) at end of study: random-effects model.

Review: Nutritional supplementation for hip fracture aftercare in older people

Comparison: 1 Multinutrient supplement (oral, nasogastric, intravenous) versus control

Outcome: 5 Unfavourable outcome (death or complications) at end of study: random-effects model

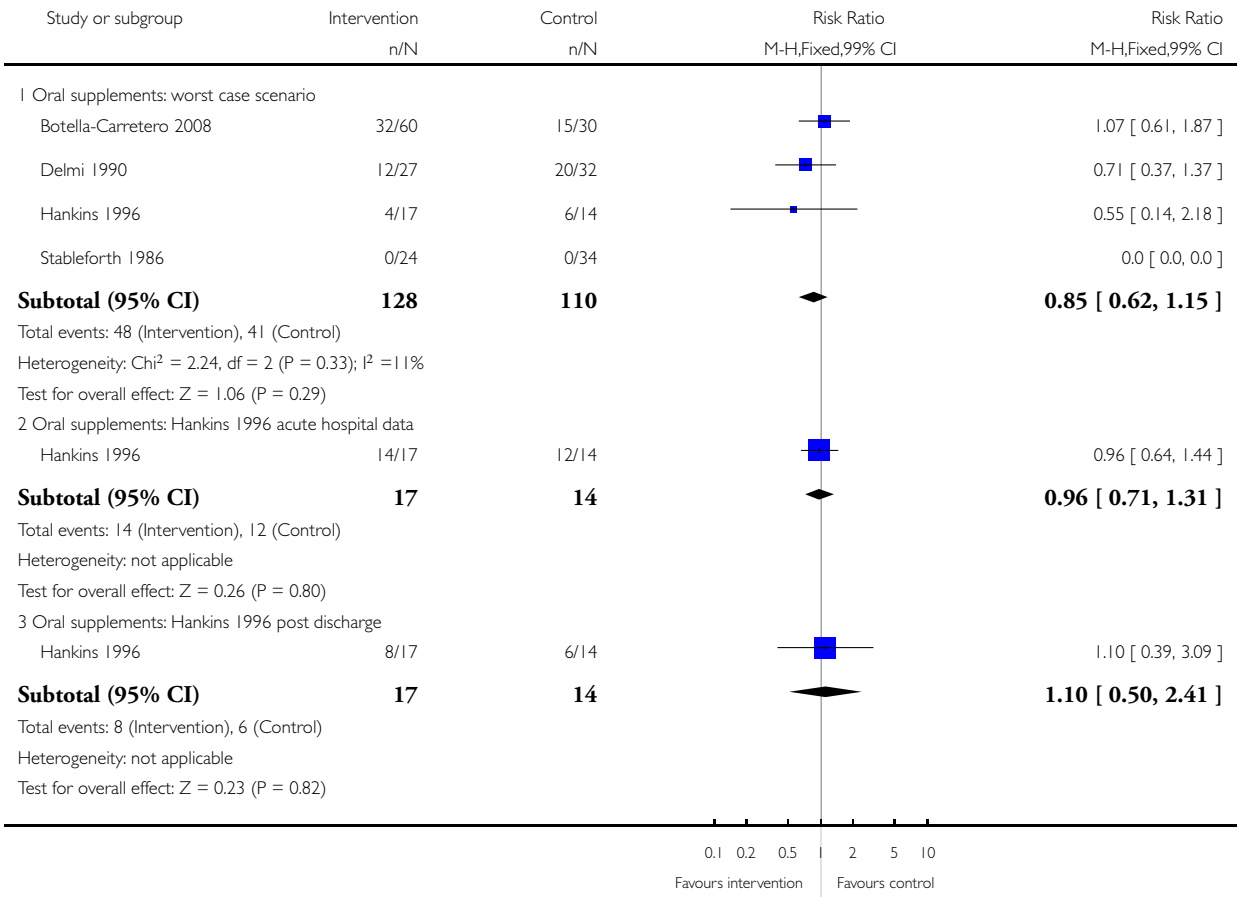


## Analysis 1.6. Comparison 1 Multinutrient supplement (oral, nasogastric, intravenous) versus control, Outcome 6 Unfavourable outcome (death or complications) - oral supplements extra analyses.

Review: Nutritional supplementation for hip fracture aftercare in older people

Comparison: 1 Multinutrient supplement (oral, nasogastric, intravenous) versus control

Outcome: 6 Unfavourable outcome (death or complications) - oral supplements extra analyses

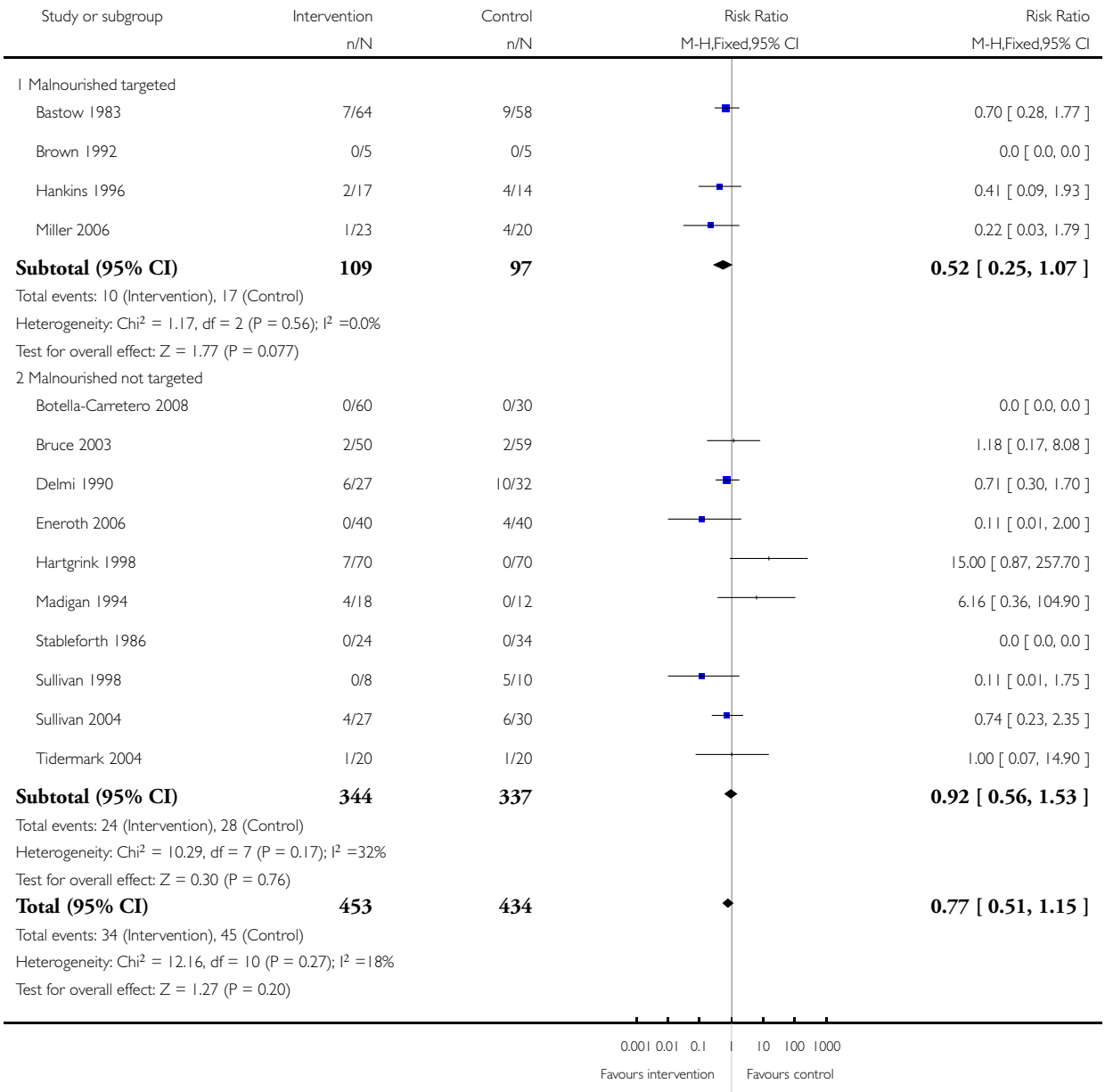


## Analysis 2.1. Comparison 2 Multinutrient supplements (oral, nasogastric routes, intravenous) versus control (split by nutritional status), Outcome 1 Mortality by end of study.

Review: Nutritional supplementation for hip fracture aftercare in older people

Comparison: 2 Multinutrient supplements (oral, nasogastric routes, intravenous) versus control (split by nutritional status)

Outcome: 1 Mortality by end of study

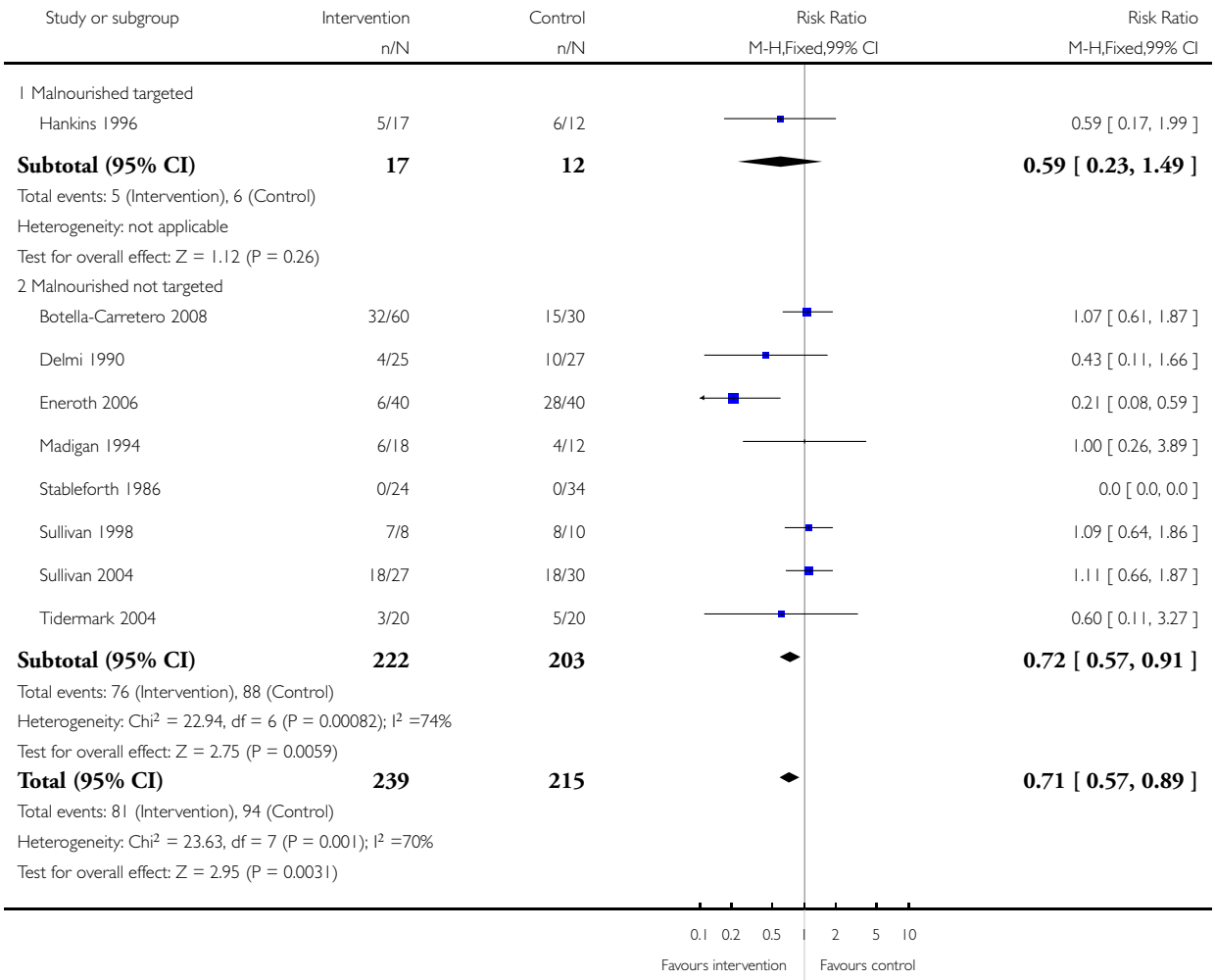


### Analysis 2.2. Comparison 2 Multinutrient supplements (oral, nasogastric routes, intravenous) versus control (split by nutritional status), Outcome 2 Patients with complications at end of study.

Review: Nutritional supplementation for hip fracture aftercare in older people

Comparison: 2 Multinutrient supplements (oral, nasogastric routes, intravenous) versus control (split by nutritional status)

Outcome: 2 Patients with complications at end of study

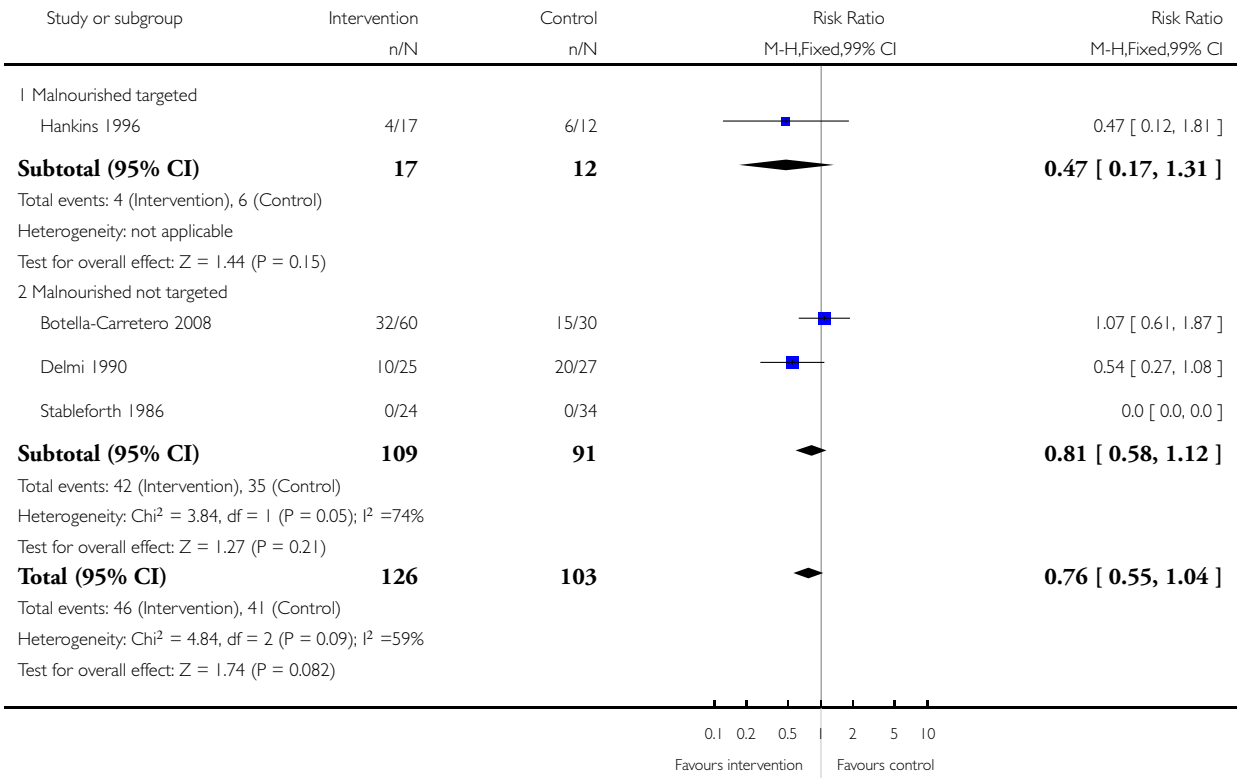


**Analysis 2.3. Comparison 2 Multinutrient supplements (oral, nasogastric routes, intravenous) versus control (split by nutritional status), Outcome 3 Unfavourable outcome (death or complications) at end of study.**

Review: Nutritional supplementation for hip fracture aftercare in older people

Comparison: 2 Multinutrient supplements (oral, nasogastric routes, intravenous) versus control (split by nutritional status)

Outcome: 3 Unfavourable outcome (death or complications) at end of study

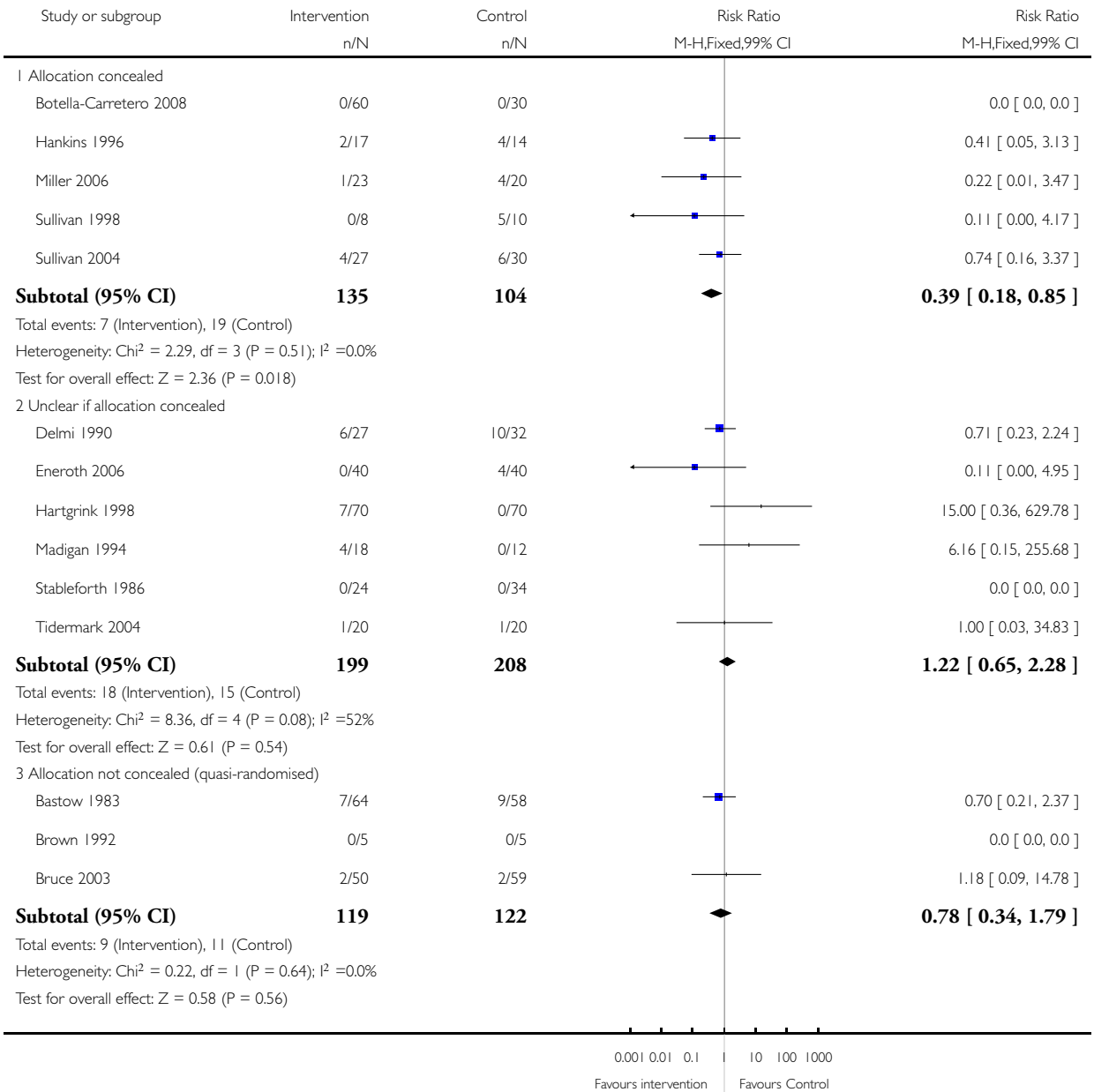


## Analysis 3.1. Comparison 3 Multinutrient supplements (oral, nasogastric routes, intravenous) versus control (by allocation concealment), Outcome 1 Mortality by end of study (concealed? = yes; unclear; no).

Review: Nutritional supplementation for hip fracture aftercare in older people

Comparison: 3 Multinutrient supplements (oral, nasogastric routes, intravenous) versus control (by allocation concealment)

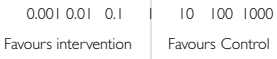
Outcome: 1 Mortality by end of study (concealed? = yes; unclear; no)




(*Continued . . .*)

(. . . *Continued*)

| Study or subgroup | Intervention n/N | Control n/N | Risk Ratio M-H,Fixed,99% CI | Risk Ratio M-H,Fixed,99% CI |
|---|---|---|---|---|
| **Total (95% CI)** | **453** | **434** | | **0.77 [ 0.51, 1.15 ]** |
| Total events: 34 (Intervention), 45 (Control) | | | | |
| Heterogeneity: Chi² = 12.16, df = 10 (P = 0.27); I² =18% | | | | |
| Test for overall effect: Z = 1.27 (P = 0.20) | | | | |




## Analysis 4.1. Comparison 4 High protein containing supplements versus low protein or non-protein containing supplements, Outcome 1 Mortality by end of study.

Review: Nutritional supplementation for hip fracture aftercare in older people

Comparison: 4 High protein containing supplements versus low protein or non-protein containing supplements

Outcome: 1 Mortality by end of study

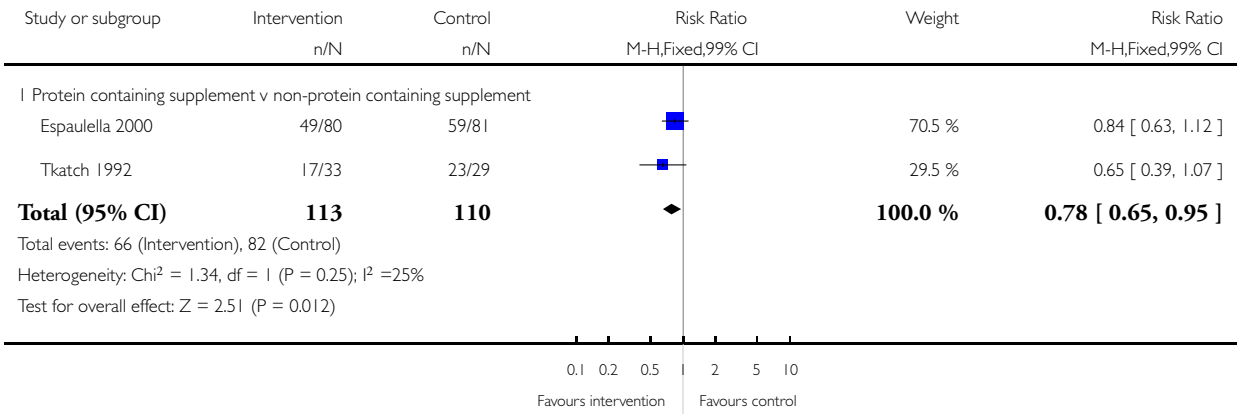
| Study or subgroup | Intervention n/N | Control n/N | Risk Ratio M-H,Fixed,99% CI | Weight | Risk Ratio M-H,Fixed,99% CI |
|---|---|---|---|---|---|
| 1 Protein containing supplement v non-protein containing supplement | | | | | |
| Espaulella 2000 | 21/85 | 13/86 | | 61.1 % | 1.63 [ 0.72, 3.71 ] |
| Schrch 1998 | 4/41 | 3/41 | | 14.2 % | 1.33 [ 0.20, 8.77 ] |
| Tkatch 1992 | 3/33 | 4/29 | | 20.1 % | 0.66 [ 0.10, 4.21 ] |
| **Subtotal (95% CI)** | **159** | **156** | | **95.5 %** | **1.38 [ 0.82, 2.34 ]** |
| Total events: 28 (Intervention), 20 (Control) | | | | | |
| Heterogeneity: Chi² = 1.34, df = 2 (P = 0.51); I² =0.0% | | | | | |
| Test for overall effect: Z = 1.22 (P = 0.22) | | | | | |
| 2 High protein containing supplement v low protein containing supplement | | | | | |
| Neumann 2004 | 2/22 | 1/24 | | 4.5 % | 2.18 [ 0.10, 46.61 ] |
| **Subtotal (95% CI)** | **22** | **24** | | **4.5 %** | **2.18 [ 0.21, 22.42 ]** |
| Total events: 2 (Intervention), 1 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.66 (P = 0.51) | | | | | |
| **Total (95% CI)** | **181** | **180** | | **100.0 %** | **1.42 [ 0.85, 2.37 ]** |
| Total events: 30 (Intervention), 21 (Control) | | | | | |
| Heterogeneity: Chi² = 1.47, df = 3 (P = 0.69); I² =0.0% | | | | | |
| Test for overall effect: Z = 1.35 (P = 0.18) | | | | | |

### Analysis 4.2. Comparison 4 High protein containing supplements versus low protein or non-protein containing supplements, Outcome 2 Unfavourable outcome (death or complications) at end of study.

Review: Nutritional supplementation for hip fracture aftercare in older people

Comparison: 4 High protein containing supplements versus low protein or non-protein containing supplements

Outcome: 2 Unfavourable outcome (death or complications) at end of study

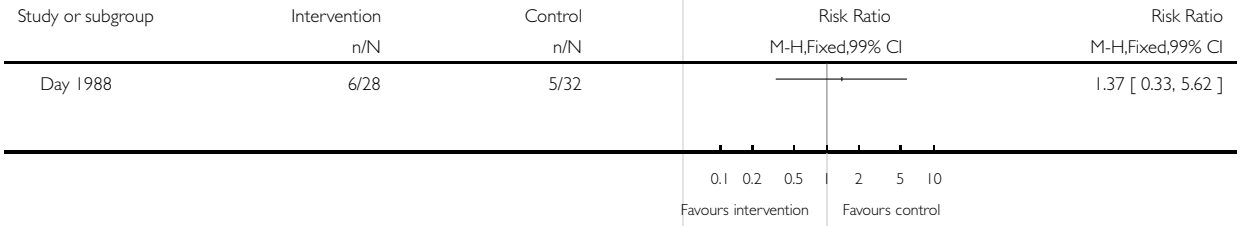



### Analysis 5.1. Comparison 5 Thiamin (vitamin B1) and water soluble vitamins versus control, Outcome 1 Mortality by end of study.

Review: Nutritional supplementation for hip fracture aftercare in older people

Comparison: 5 Thiamin (vitamin B1) and water soluble vitamins versus control

Outcome: 1 Mortality by end of study

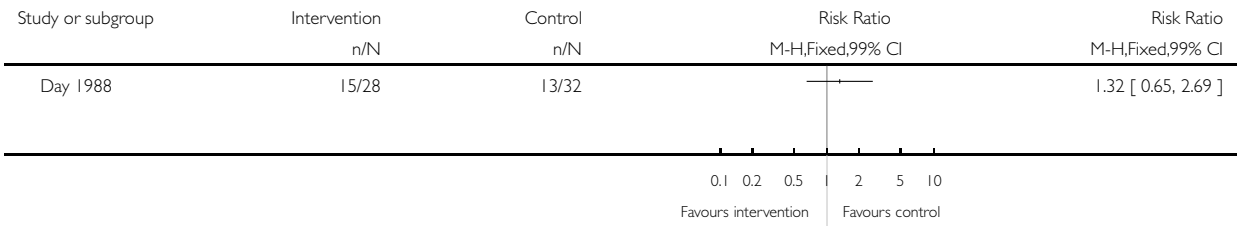


**Analysis 5.2. Comparison 5 Thiamin (vitamin B1) and water soluble vitamins versus control, Outcome 2 Patients with complications at end of study.**

Review: Nutritional supplementation for hip fracture aftercare in older people

Comparison: 5 Thiamin (vitamin B1) and water soluble vitamins versus control

Outcome: 2 Patients with complications at end of study

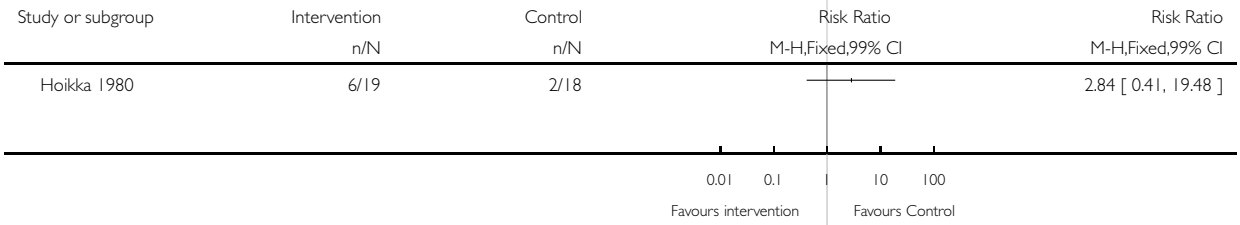



**Analysis 6.1. Comparison 6 Vitamin D versus control, Outcome 1 Patients with complications at end of study.**

Review: Nutritional supplementation for hip fracture aftercare in older people

Comparison: 6 Vitamin D versus control

Outcome: 1 Patients with complications at end of study



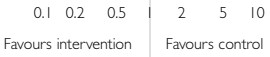
### Analysis 7.1. Comparison 7 Dietetic assistants versus usual care, Outcome 1 Mortality by end of study.

Review: Nutritional supplementation for hip fracture aftercare in older people

Comparison: 7 Dietetic assistants versus usual care

Outcome: 1 Mortality by end of study

| Study or subgroup | Intervention n/N | Control n/N | Risk Ratio M-H,Fixed,99% CI | Risk Ratio M-H,Fixed,99% CI |
|---|---|---|---|---|
| Duncan 2006 | 19/145 | 36/157 | | 0.57 [ 0.29, 1.11 ] |



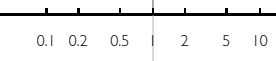

### Analysis 7.2. Comparison 7 Dietetic assistants versus usual care, Outcome 2 Patients with complications at end of study.

Review: Nutritional supplementation for hip fracture aftercare in older people

Comparison: 7 Dietetic assistants versus usual care

Outcome: 2 Patients with complications at end of study

| Study or subgroup | Intervention n/N | Control n/N | Risk Ratio M-H,Fixed,99% CI | Risk Ratio M-H,Fixed,99% CI |
|---|---|---|---|---|
| Duncan 2006 | 79/130 | 84/125 | | 0.90 [ 0.71, 1.15 ] |



# APPENDICES

## Appendix 1. Search strategies

### MEDLINE (Ovid)

1. exp fractures/
2. fracture$.tw
3. exp decubitus ulcer/
4. decubitus ulcer$.tw
5. pressure sore$. Tw
6. orthop$.tw
7. or/1-6
8. exp food/
9. food$.tw
10. diet$.tw
11. exp diet/
12. exp diet therapy/
13. exp nutrition/
14. nutri$.tw
15. exp nutrition disorders/
16. exp nutritional support/
17. supplement$.tw
18. weigh$.tw
19. exp body weight/
20. exp dietary fats/
21. exp dietary proteins/
22. exp dietary carbohydrates/
23. or/8-22
24. exp calcium, dietary/
25. exp phosphorus, dietary/
26. exp magnesium/
27. magnesium.tw
28. exp potassium, dietary/
29. exp sodium, dietary/
30. chloride$.tw
31. exp sulfur/
32. sulphate$.tw
33. sulfate$.tw
34. exp iron, dietary/
35. exp fluoride/
36. fluoride$.tw
37. exp trace elements/
38. trace element$.tw
39. trace metal$.tw
40. micronutrient$.tw
41. zinc.tw
42. copper.tw
43. selen$.tw
44. manganese.tw
45. molybdenum.tw
46. chromium.tw

47. cobalt.tw
48. iodi#e$.tw
49. or/24-48
50. exp vitamins/
51. vitamin$.tw
52. ascorb$.tw
53. thiamin$.tw
54. riboflavin$.tw
55. pyridox$.tw
56. niacin$.tw
57. fola$.tw
58. folic.tw
59. biotin.tw
60. cobalamin$.tw
61. retino$.tw
62. exp carotenoid/
63. caroten$.tw
64. tocopher$.tw
65. dihydrotachysterol.tw
66. calcitriol.tw
67. cholecalciferol.tw
68. alfacalcidol.tw
69. alphacalcidol.tw
70. or/50-69
71. or/23,49,70
72. and/7,71
73. Randomized Controlled Trial.pt.
74. Controlled Clinical Trial.pt.
75. Random Allocation/
76. Double Blind Method/
77. Single Blind Method/
78. exp Cross-Over Studies/
79. or/73-78
80. ((clinical or controlled or comparative or placebo or prospective or randomi#ed) adj3 (trial or study)).tw
81. (random$ adj7 (allocat$ or allot$ or assign$ or basis$ or divid$ or order$)).tw
82. ((singl$ or doubl$ or trebl$ or tripl$) adj7 (blind$ or mask$)).tw
83. ((cross?over$ or (cross adj1 over$)).tw
84. ((allocat$ or allot$ or assign$ or divid$) adj3 (condition$ or experiment$ or intervention$ or treatment$ or therap$ or control$ or group$)).tw
85. or/80-84
86. or/79,85
87. and/72,86

### EMBASE (Ovid)

1. exp fractures/
2. fracture$.tw
3. exp decubitus ulcer/
4. decubitus ulcer$.tw
5. pressure sore$. tw
6. orthop$.tw
7. or/1-6
8. exp food/

9. food$.tw
10. diet$.tw
11. exp diet/
12. exp diet therapy/
13. exp nutrition/
14. nutri$.tw
15. exp nutrition disorders/
16. exp nutritional support/
17. supplement$.tw
18. weigh$.tw
19. exp body weight/
20. exp dietary fats/
21. exp dietary proteins/
22. exp dietary carbohydrates/
23. or/8-22
24. exp calcium, dietary/
25. exp phosphorus, dietary/
26. exp magnesium/
27. magnesium.tw
28. exp potassium, dietary/
29. exp sodium, dietary/
30. chloride$.tw
31. exp sulfur/
32. sulphate$.tw
33. sulfate$.tw
34. exp iron, dietary/
35. exp fluoride/
36. fluoride$.tw
37. exp trace elements/
38. trace element$.tw
39. trace metal$.tw
40. micronutrient$.tw
41. zinc.tw
42. copper.tw
43. selen$.tw
44. manganese.tw
45. molybdenum.tw
46. chromium.tw
47. cobalt.tw
48. iodi#e$.tw
49. or/24-48
50. exp vitamins/
51. vitamin$.tw
52. ascorb$.tw
53. thiamin$.tw
54. riboflavin$.tw
55. pyridox$.tw
56. niacin$.tw
57. fola$.tw
58. folic.tw
59. biotin.tw
60. cobalamin$.tw
61. retino$.tw

62. exp carotenoid/
63. caroten$.tw
64. tocopher$.tw
65. dihydrotachysterol.tw
66. calcitriol.tw
67. cholecalciferol.tw
68. alfacalcidol.tw
69. alphacalcidol.tw
70. or/50-69
71. or/23,49,70
72. and/7,71
73. clinical trial/
74. Multicenter Study/
75. phase 2 clinical trial/
76. phase 3 clinical trial/
77. phase 4 clinical trial/
78. Randomized Controlled Trial/
79. controlled study/
80. meta analysis/
81. crossover procedure/
82. double blind procedure/
83. single blind procedure/
84. randomization/
85. Major Clinical Study/
86. placebo/
87. drug comparison/
88. clinical study/
89. (clin$ adj25 trial$).tw
90. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).tw
91. placebo$.tw
92. random$.tw
93. control$.tw
94. or/73-93
95. and/72,94

### Nutrition Abstracts and Reviews (Ovid)

1. exp fractures/
2. fracture$.tw
3. decubitus ulcer$.tw
4. pressure sore$.tw
5. orthop$.tw
6. or/1-5
7. dog$.tw
8. bird$.tw
9. horse$.tw
10. soil$.tw
11. wood$.tw
12. freeze fracture$.tw
13. or/7-12
14. random$.tw
15. trial$.tw
16. placebo$.tw

17. or/14-16
18. and/6,17
19. 18 not 13

## WHAT'S NEW

Last assessed as up-to-date: 28 February 2009.

| | | |
|---|---|---|
| 12 November 2009 | New citation required and conclusions have changed | In this sixth update, published in Issue 1, 2010 of *The Cochrane Library*, we updated our trial search to September 2008. Of the 10 newly identified studies for this update, one trial is included (Botella-Carretero 2008), five trials are excluded (Boudville 2002; Hommel 2007; Kacmaz 2007; Oloffson 2007; Thomas 2008) and one trial awaits classification ( Gerstorfer 2008). Three new trials are ongoing ( Dagnelie; Houdijk; Miller). Of previously identified trials: one former ongoing trial is now included ( Eneroth 2006), and one trial formerly awaiting classification (Miller 2006) is now included. A new category (intravenous feeding and oral supplements)was set up for one new trial.<br>There was slight modification to the conclusions that reflected reappraisal of the available evidence. |

## HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 1, 2000

| | | |
|---|---|---|
| 15 August 2008 | Amended | Converted to new review format. |
| 4 August 2006 | New search has been performed | In the fifth update, published in *The Cochrane Library* Issue 4, 2006, we updated our trial search to January 2006. Of the six newly identified studies for this update, one trial is included (Sullivan 2004), three trials are excluded (Ashworth 2006; Carlsson 2005; Wong 2004) and two trials await assessment (Eneroth 2005; Stratton 2005). Of two former ongoing trials, one is now included (Duncan 2006, formerly Johansen 2002) and the other awaits assessment (Miller 2006, formerly Crotty 2003). One trial formerly awaiting assessment is now included (Neumann 2004). Two existing categories were modified to accommodate two newly included trials. A new category (dietetic assistants versus usual care) was set up for the third new trial. |

(*Continued*)

| | | |
|---|---|---|
| 3 November 2003 | New search has been performed | In the fourth update, published in *The Cochrane Library* Issue 1, 2004, we updated our trial search to August 2003. Two new trials were included (Bruce 2003; Houwing 2003). Two newly identified trials were excluded (Hedström 2002; Stumm 2001). One newly identified trial is awaiting assessment (Tidermark 2003). Updates to all three ongoing trials were provided (Cameron 2000; Crotty 2003; Johansen 2002). The review conclusions were unchanged. |
| 1 May 2002 | New search has been performed | In the third update, published in Issue 3, 2002 of *The Cochrane Library*, we updated our trial search to April 2002. No new trials were included. Two newly identified trials were excluded (Bachrach 2001; Lauque 2000). Four trials previously awaiting assessment were now excluded. Two newly identified trials (Crotty 2003; Johansen 2002) were included as ongoing trials. The review conclusions were unchanged. |
| 1 May 2001 | New search has been performed | In the second update, published in Issue 3, 2001 of *The Cochrane Library*, the trial search was updated to April 2001. No new trials were included. Two more trials were excluded: one previously awaiting assessment (Doshi 1998) on the basis of a full journal publication (Lawson 2000) and the other (Bachrach 2000) was newly identified. One newly identified trial, only available as a conference abstract, was placed in Studies awaiting assessment (Moller-Madsen 1988) and further details sought. The review conclusions were unchanged. |
| 1 August 2000 | New search has been performed | In the first update, published in Issue 4, 2000 of *The Cochrane Library*, we extended our trial search to January 2000. We identified one new ongoing trial (Cameron 2000), and obtained new information on four included trials and two studies placed in the awaiting assessment category in the first version of this review. This extra information resulted in one included trial (Williams 1989) being excluded, and one of the two studies pending assessment being included (Espaulella 2000) and the other excluded (Pedersen 1999).<br>The inclusion of the new trial, which evaluated the effect of protein in an oral feed, and the other new information did not substantially alter the conclusions of the original review.<br>Relative risks instead of Peto odds ratios were presented for dichotomous outcomes. Again, this did not affect the conclusions of the review. |

## CONTRIBUTIONS OF AUTHORS

Alison Avenell initiated the review, wrote the first draft of the protocol, undertook the subject-specific literature search, contacted trialists and wrote the first drafts of the review and updates. Both authors assessed and extracted data from trials and devised the analyses. Helen Handoll provided methodological support at all stages and critically rewrote the review and updates. Alison Avenell and Helen Handoll are the guarantors of the review.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT


### Internal sources

- University of Teesside, Middlesbrough, UK.
- University of Aberdeen, UK.

### External sources

- Chief Scientist Office of the Scottish Government Health Directorates, UK.


## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None known.

## INDEX TERMS

### Medical Subject Headings (MeSH)

*Aftercare; *Dietary Supplements; Hip Fractures [*complications]; Malnutrition [*diet therapy]; Nutritional Support [*methods]; Randomized Controlled Trials as Topic

### MeSH check words

Aged; Humans