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[Intervention Review]

Nutritional interventions for preventing and treating pressure ulcers

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ABSTRACT

Background

Pressure ulcers are localized injuries to the skin or the underlying tissue, or both, and are common in older and immobile people, people with diabetes, vascular disease, or malnutrition, as well as those who require intensive or palliative care. People with pressure ulcers often suffer from severe pain and exhibit social avoidance behaviours. The prevention and treatment of pressure ulcers involves strategies to optimize hydration, circulation, and nutrition. Adequate nutrient intake can reduce the risk factor of malnutrition and promote wound healing in existing pressure ulcers. However, it is unclear which nutrients help prevent and treat pressure ulcers. This is an update of an earlier Cochrane Review.

Objectives

To evaluate the benefits and harms of nutritional interventions (special diets, supplements) for preventing and treating pressure ulcers in people with or without existing pressure ulcers compared to standard diet or other nutritional interventions.

Search methods

We used extensive Cochrane search methods. The latest search was in May 2022.

Selection criteria

We included randomized controlled trials (RCTs) in people with or without existing pressure ulcers, that compared nutritional interventions aimed at preventing or treating pressure ulcers with standard diet or other types of nutritional interventions.

Data collection and analysis

We used standard Cochrane methods. Our primary outcome for prevention studies was the proportion of participants who developed new (incident) pressure ulcers. For treatment studies, our primary outcomes were time to complete pressure ulcer healing, number of people with healed pressure ulcers, size and depth of pressure ulcers, and rate of pressure ulcer healing. Secondary outcomes were side effects, costs, health-related quality of life and acceptability. We used GRADE to assess certainty of evidence for each outcome.

Main results

We included 33 RCTs with 7920 participants. Data for meta-analysis were available from 6993 participants.

Pressure ulcer prevention

Eleven studies (with 12 arms) compared six types of nutritional interventions for the prevention of pressure ulcers.

Compared to standard diet, energy, protein and micronutrient supplements may result in little to no difference in the proportion of participants developing a pressure ulcer (energy, protein and micronutrient supplements 248 per 1000, standard diet 269 per 1000; RR 0.92, 95% CI 0.71 to 1.19; 3 studies, 1634 participants; low-certainty evidence).

Compared to standard diet, protein supplements may result in little to no difference in pressure ulcer incidence (protein 21 per 1000, standard diet 28 per 1000; RR 0.75, 95% CI 0.49 to 1.14; 4 studies, 4264 participants; low-certainty evidence). The evidence is very uncertain about the gastrointestinal side effects of these supplements (protein 109 per 1000, standard diet 155 per 1000; RR 0.70, 95% CI 0.06 to 7.96; 2 studies, 140 participants, very low-certainty evidence).

The evidence is very uncertain about the effects of protein, arginine, zinc and antioxidants; L-carnitine, L-leucine, calcium, magnesium and vitamin D; EPA, GLA and antioxidants; disease-specific supplements on pressure ulcer incidence when compared to standard diet (1 study each; very low-certainty evidence for all comparisons).

Pressure ulcer treatment

Twenty-four studies (with 27 arms) compared 10 types of nutritional interventions or supplements for treatment of pressure ulcers.

Compared to standard diet, energy, protein and micronutrient supplements may slightly increase the number of healed pressure ulcers (energy, protein and micronutrients 366 per 1000, standard diet 253 per 1000; RR 1.45, 95% CI 1.14 to 1.85; 3 studies, 577 participants, low-certainty evidence). The evidence is very uncertain about the effect of these supplements on gastrointestinal side effects.

Compared to standard diet, the evidence is very uncertain about the effect of protein, arginine, zinc and antioxidant supplements on pressure ulcer healing (pressure ulcer area: mean difference (MD) 2 cm^2 smaller, 95% CI 4.54 smaller to 0.53 larger; 2 studies, 71 participants, very low-certainty evidence). The evidence on side effects of these supplements is very uncertain.

Compared to standard diet, supplements with arginine and micronutrients may not increase the number of healed pressure ulcers, but the evidence suggests a slight reduction in pressure ulcer area (MD 15.8% lower, 95% CI 25.11 lower to 6.48 lower; 2 studies, 231 participants, low-certainty evidence). The evidence is very uncertain about changes in pressure ulcer scores, acceptability, and side effects of these supplements.

Compared to placebo, collagen supplements probably improve the mean change in pressure ulcer area (MD 1.81 cm^2 smaller, 95% CI 3.36 smaller to 0.26 smaller; 1 study, 74 participants, moderate-certainty evidence). The evidence is very uncertain about the effect of these supplements on side effects.

The evidence is very uncertain about the effects of vitamin C, different doses of arginine; EPA, GLA (special dietary fatty acids) and antioxidants; protein; a specialized amino acid mixture; ornithine alpha-ketoglutarate and zinc supplements on pressure ulcer healing (1 or 2 studies each; very low-certainty evidence).

Authors' conclusions

The benefits of nutritional interventions with various compositions for pressure ulcer prevention and treatment are uncertain. There may be little or no difference compared to standard nutrition or placebo. Nutritional supplements may not increase gastrointestinal side effects, but the evidence is very uncertain. Larger studies with similar nutrient compositions would reduce these uncertainties. No study investigated the effects of special diets (e.g. protein-enriched diet, vegetarian diet) on pressure ulcer incidence and healing.

PLAIN LANGUAGE SUMMARY

Which diets or supplements are most effective for preventing and treating pressure ulcers and do they cause unwanted effects?

Key messages

• Due to a lack of robust evidence, the benefits and unwanted effects of most diets and supplements for the prevention and treatment of pressure ulcers are unclear.

• Energy, protein and micronutrients; protein, arginine, zinc and antioxidants; arginine and micronutrients; and collagen supplements may be better than a standard diet alone for healing pressure ulcers.

• We need more and better studies with larger samples, and longer follow-up times, which examine the same outcomes, to determine the real effect of nutritional interventions for the prevention and treatment of pressure ulcers.

What are nutritional interventions?

Nutritional interventions are special meals or supplementary food in addition to a person's normal diet to help with general health or specific conditions. They may be extra calories, macronutrients (like proteins) or micronutrients (like vitamins or minerals). They can be given by mouth or through a tube (called tube feeding). They can also be given via an infusion or injection (parenteral nutrition).

Why is nutrition important for people with pressure ulcers or at risk of developing pressure ulcers?

Pressure ulcers are also known as pressure sores, bedsores and decubitus ulcers. They are an injury to the skin or underlying tissue, or both, caused by pressure, shear and friction. Pressure on the skin reduces circulation; shear is when layers of skin and tissue slide over one another, when the patient moves in bed, for example; and friction is when the skin rubs against bedsheets or clothing. Pressure ulcers usually form on bony parts of the body, such as the heels or tail bone. People who are immobilized, by a fall or surgery, for example, or who have conditions like diabetes or vascular disease are at risk of getting pressure ulcers. If they have poor nutrition, they may be at greater risk of getting pressure ulcers and these may be more severe.

What did we want to find out?

We wanted to know whether nutritional interventions help to prevent people developing pressure ulcers and to promote the healing of existing pressure ulcers.

We were interested in the effect of nutritional interventions on:

• the development or healing of pressure ulcers

• possible unwanted effects experienced by individuals

• individual quality of life

What did we do?

We searched for studies that investigated any form of nutritional intervention compared with a normal diet, placebo (dummy medicine) or another type of nutritional intervention. We compared and summarized the results of studies that examined similar nutritional interventions and assessed our confidence in the evidence based on factors such as study methods and sample sizes.

What did we find?

We found 33 studies that involved 7920 people. Eleven studies looked at the effects of nutritional interventions on preventing pressure ulcers and 24 studies evaluated nutritional interventions for treating pressure ulcers. Amongst those, two studies investigated the effects on both preventing and treating pressure ulcers.

Main results

Preventing pressure ulcers in people at risk of getting them

• Energy, protein and micronutrient supplements may make little to no difference to the development of a pressure ulcer (3 studies, 1634 people).

• A protein supplement may make little to no difference in pressure ulcer development (4 studies, 4264 people). It is unclear if the protein supplement causes any unwanted effects.

• it is unclear if other supplements have an effect on pressure ulcer development.

Treating people with pressure ulcers

• Energy, protein and micronutrient supplements may increase the number of people whose pressure ulcers healed, but we are very uncertain about this result (3 studies, 577 people). It is unclear if the energy, protein and micronutrient supplements cause any unwanted effects.

• Compared to a standard diet, we are uncertain whether protein, arginine, zinc and antioxidant supplements improve the healing of pressure ulcers, (2 studies, 71 people). We do not know if protein, arginine, zinc and antioxidant supplements cause any unwanted effects.

• Arginine and micronutrient supplements may not increase the number of pressure ulcers healed, but they may slightly increase pressure ulcer healing (2 studies, 231 people). It is unclear if the intervention has an effect on acceptability and unwanted effects.

• Collagen supplements probably increase pressure ulcer healing (1 study, 74 people). The intervention may increase unwanted effects, but we are very uncertain about this result.

• it is unclear if other supplements have an effect on the healing of pressure ulcers.

What are the limitations of the evidence?

We have little to very little confidence in our findings because many of the studies were small, of low quality, and did not provide data on everything we were interested in. About half of the studies were funded or supported by pharmaceutical companies, which might have influenced the results. We could not use data from studies about some types of nutritional interventions because the diet or supplement was only examined in one study.

How up to date is this review?

The review is up to date to May 2022.

Summary of findings 1. Summary of findings table - Energy, protein and micronutrients compared to standard diet for the prevention of pressure ulcers

Energy, protein and micronutrients compared to standard diet for the prevention of pressure ulcers

Patient or population: inpatients who are mildly or seriously malnourished or at risk of being malnourished, elderly patients at risk of developing pressure ulcers
Setting: hospitals in Uruguay and France, and university hospital long-term care clinic in Sweden
Intervention: energy, protein and micronutrients
Comparison: standard diet

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard diet	Risk with energy, protein and micronutrients				
Incidence of pressure ulcers follow-up: range 2 to 26 weeks	269 per 1000	**248 per 1000** (191 to 321)	**RR 0.92** (0.71 to 1.19)	1634 (3 RCTs)	⊕⊕⊖⊖ Low[a]	
Time to pressure ulcer development - not reported	-	-	-	-	-	
Acceptability of nutritional supplements - not reported	-	-	-	-	-	
Side effects - not reported	-	-	-	-	-	
Costs - not reported	-	-	-	-	-	
Health-related quality of life - not reported	-	-	-	-	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_434471802060513226.

[a] Downgraded by two levels for risk of bias since we rated all included studies at overall high risk of bias.

Summary of findings 2. Summary of findings table - Protein compared to standard diet for the prevention of pressure ulcers

Protein compared to standard diet for the prevention of pressure ulcers

Patient or population: patients (> 65 years) following hip fracture; patients with a recent stroke
Setting: hospitals in Israel, Spain, The Netherlands, Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, Hong Kong, India, Italy, New Zealand, Poland, Portugal, Republic of Ireland, Turkey, and UK
Intervention: protein
Comparison: standard diet

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard diet	Risk with protein				
Incidence of pressure ulcers follow-up: range 1 days to 14 days	28 per 1000	**21 per 1000** (14 to 32)	**RR 0.75** (0.49 to 1.14)	4264 (4 RCTs)	⊕⊕⊖⊖ Low[a,b]	
Time to pressure ulcer development - not reported	-	-	-	-	-	
Acceptability of nutritional supplements - not reported	-	-	-	-	-	
Side effects: at least one adverse gastrointestinal event follow-up: range 1 days to 14 days	155 per 1000	**109 per 1000** (9 to 1000)	**RR 0.70** (0.06 to 7.96)	140 (2 RCTs)	⊕⊖⊖⊖ Very low[c,d]	
Costs - not reported	-	-	-	-	-	
Health-related quality of life - not reported	-	-	-	-	-	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_434471846697869273.

[a] Downgraded by one level for risk of bias since our rating for overall risk of bias for three of the four included studies was some concerns.
[b] Downgraded by one level for imprecision since the 95% CI overlaps the null effect and includes potential benefit (RR < 0.75), and the number of events was low (n = 99).
[c] Downgraded by one level for risk of bias since we rated the two included studies as some concerns.
[d] Downgraded by two levels for imprecision since the 95% CI overlaps the null effect and includes potential benefit (RR < 0.75) and potential harm (RR > 1.25), and also a very low number of events (n = 26) and participants (n = 140).

Summary of findings 3. Summary of findings table - Energy, protein and micronutrients compared to standard diet for treating pressure ulcers

Energy, protein and micronutrients compared to standard diet for treating pressure ulcers

Patient or population: long-term care patients; inpatients without dehydration with energy intake by tube feeding; patients with pressure ulcers
Setting: hospitals in Japan and China, and long-term care clinic in Sweden
Intervention: energy, protein and micronutrients
Comparison: standard diet

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard diet	Risk with energy, protein and micronutrients				
Pressure ulcers healed follow-up: range 3 to 26 weeks	253 per 1000	**366 per 1000** (288 to 467)	**RR 1.45** (1.14 to 1.85)	577 (3 RCTs)	⊕⊕⊖⊖ Low[a]	
Time to complete healing of pressure ulcers - not reported	-	-	-	-	-	
Change in area/depth/volume of pressure ulcers - not reported	-	-	-	-	-	
Acceptability of nutritional supplements - not reported	-	-	-	-	-	

Side effects: at least one adverse gastrointestinal event follow-up: range 1 to 12 weeks	167 per 1000	**267 per 1000** (98 to 722)	**RR 1.60** (0.59 to 4.33)	60 (1 RCT)	⊕⊖⊖⊖ Very low[b,c]
Costs - not reported	-	-	-	-	-
Health-related quality of life - not reported	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_434471852050587612.

[a] Downgraded by two levels for risk of bias since we rated all included studies at overall high risk of bias.
[b] Downgraded by one level for risk of bias since we rated the included study at overall high risk of bias.
[c] Downgraded by two levels for imprecision since the 95% CI overlaps the null effect and includes potential benefit (RR < 0.75) and potential harm (RR > 1.25), and also a very low number of events (n = 13) and participants (n = 60).

Summary of findings 4. Summary of findings table - Protein, arginine, zinc and antioxidants compared to standard diet or placebo for treating pressure ulcers

Protein, arginine, zinc and antioxidants compared to standard diet or placebo for treating pressure ulcers

Patient or population: residents of long-term care (≥ 65 years) with pressure ulcers; inpatients with pressure ulcers
Setting: long-term care facilities in Italy, and healthcare centres, hospitals, and long-term care facilities in Czech Republic, Belgium, The Netherlands, and Curacao
Intervention: protein, arginine, zinc and antioxidants
Comparison: standard diet or placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard diet or placebo	Risk with protein, arginine, zinc and antioxidants				

Pressure ulcers healed follow-up: 8 weeks	161 per 1000	**202 per 1000** (79 to 508)	**RR 1.25** (0.49 to 3.15)	61 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b]
Time to complete healing of pressure ulcers - not reported	-	-	-	-	-
Pressure ulcer area (absolute) follow-up: 8 weeks	The mean pressure ulcer area (absolute) ranged from **3.34 to 12.28** cm^2	MD **2 cm^2 lower** (4.54 lower to 0.53 higher)	-	71 (2 RCTs)	⊕⊖⊖⊖ Very low[a,c]
Acceptability of nutritional supplements - not reported	-	-	-	-	-
Side effects: at least one adverse gastrointestinal event follow-up: 8 weeks	619 per 1000	**724 per 1000** (477 to 1000)	**RR 1.17** (0.77 to 1.79)	43 (1 RCT)	⊕⊖⊖⊖ Very low[d,e]
Costs - not reported	-	-	-	-	-
Health-related quality of life - not reported	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_4344718612303462O7.

[a] Downgraded by one level for risk of bias since we rated the higher weighted study (out of two) at overall risk of bias of some concerns.
[b] Downgraded by two levels for imprecision since the 95% CI overlaps the null effect and includes potential benefit (RR < 0.75) and potential harm (RR > 1.25), and also a very low number of events (n = 12) and participants (n = 61).
[c] Downgraded by two levels for imprecision since the 95% CIs are wide, and the number of participants was low (n = 71).
[d] Downgraded by one level for risk of bias since we rated the included study at overall risk of bias of some concerns.
[e] Downgraded by two levels for imprecision since the 95% CI overlaps the null effect and includes potential benefit (RR < 0.75) and potential harm (RR > 1.25), and also a very low number of events (n = 29) and participants (n = 43).

Summary of findings 5. Summary of findings table - Arginine and micronutrients compared to standard diet for treating pressure ulcers

Arginine and micronutrients compared to standard diet for treating pressure ulcers

Patient or population: malnourished patients with pressure ulcers
Setting: hospital in Japan, tertiary referral hospital in Australia, and long-term care and home-care services in Italy
Intervention: arginine and micronutrients
Comparison: standard diet

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard diet	Risk with arginine and micronutrients				
Pressure ulcers healed follow-up: 8 weeks	101 per 1000	**169 per 1000** (81 to 349)	**RR 1.67** (0.80 to 3.46)	200 (1 RCT)	⊕⊕⊖⊖ Low[a]	
Time to complete healing of pressure ulcers - not reported	-	-	-	-	-	
Change in pressure ulcer area (cm^2) follow-up: range 4 weeks to 8 weeks	The mean change in pressure ulcer area (cm^2) was **-0.45** cm^2	MD **3.25 cm^2 lower** (7.19 lower to 0.69 higher)	-	31 (1 RCT)	⊕⊕⊖⊖ Low[b,c]	Several measures (cm^2 and percentage) of the same outcome (change in pressure ulcer area) due to different studies.
Change in pressure ulcer area (percentage) follow-up: 8 weeks	The mean change in pressure ulcer area (percentage) ranged from **-3.32 to -45.2** %	MD **15.8 % lower** (25.11 lower to 6.48 lower)	-	231 (2 RCTs)	⊕⊕⊖⊖ Low[b,c]	
Acceptability of nutritional supplements: non-adherence	0 per 1000	**0 per 1000** (0 to 0)	**RR 15.60** (0.94 to 259.00)	49 (1 RCT)	⊕⊖⊖⊖ Very low[d,e]	
Side effects: at least one adverse gastrointestinal event follow-up: range 3 weeks to 8 weeks	21 per 1000	**33 per 1000** (8 to 142)	**RR 1.54** (0.36 to 6.64)	282 (3 RCTs)	⊕⊖⊖⊖ Very low[f,g]	
Costs (EUR) follow-up: 8 weeks	The mean costs (EUR) was **173.40**	MD **39.4 higher**	-	138 (1 RCT)	⊕⊕⊕⊖ Moderate[h]	

		(27.57 higher to 51.23 higher)			
Health-related quality of life - not reported	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_434471869054558178.

[a] Downgraded by two levels for imprecision since the 95% CI overlaps the null effect and includes nearly potential benefit (RR < 0.75) and potential harm (RR > 1.25), and also a low number of events (n = 27) and participants (n = 200).
[b] Downgraded by one level for risk of bias since we rated the included study at overall high risk of bias.
[c] Downgraded by one level for imprecision; the 95% CI was narrow but the number of participants was low (n = 31 and n = 231).
[d] Downgraded by one level for risk of bias since we rated the included study at overall high risk of bias.
[e] Downgraded by two levels for imprecision since the 95% CIs are wide, and the number of participants was very low (n = 31 and n = 49).
[f] Downgraded by one level for risk of bias since we rated one of the three included studies at overall high risk of bias.
[g] Downgraded by two levels for imprecision since the 95% CI overlaps the null effect and includes potential benefit (RR < 0.75) and potential harm (RR > 1.25), and also a very low number of events (n = 10) and participants (n = 311).
[h] Downgraded by one level for imprecision; the 95% CI did not overlap the null effect but the number of participants was low (n = 138).

Summary of findings 6. Summary of findings table - Collagen compared to standard diet or placebo for treating pressure ulcers

Collagen compared to standard diet or placebo for treating pressure ulcers

Patient or population: adult inpatients or outpatients with pressure ulcers
Setting: hospitals in India and Japan
Intervention: collagen
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Risk with placebo	Risk with collagen			
Pressure ulcers healed - not reported	-	-	-	-	-
Time to complete healing of pressure ulcers - not reported	-	-	-	-	-
Change in pressure ulcer area (cm^2) follow-up: 16 weeks	The mean change in pressure ulcer area (cm^2) was **5** cm^2	MD **1.81 cm^2 lower** (3.36 lower to 0.26 lower)	-	74 (1 RCT)	⊕⊕⊕⊖ Moderate[a]
Acceptability of nutritional supplements - not reported	-	-	-	-	-
Side effects: at least one adverse event follow-up: range 4 weeks to 16 weeks	17 per 1000	**46 per 1000** (6 to 384)	**RR 2.69** (0.33 to 22.30)	154 (2 RCTs)	⊕⊖⊖⊖ Very low[b,c]
Costs - not reported	-	-	-	-	-
Health-related quality of life - not reported	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_434471894103728107.

[a] Downgraded by one level for imprecision; the 95% CI was narrow and did not overlap the null effect but the number of participants was low (n = 74).
[b] Downgraded by one level for risk of bias since we rated the included studies at overall risk of bias of some concerns.
[c] Downgraded by two levels for imprecision since the 95% CI overlaps the null effect and includes potential benefit (RR < 0.75) and potential harm (RR > 1.25), and a very low number of events (n = 6) and participants (n = 154).

BACKGROUND

Pressure ulcers affect a significant minority of people in hospitals and other care facilities. International studies show pressure ulcer prevalence rates in hospitals ranging from 2.2% to 24.7% (Eglseer 2019; Kasikci 2018; Li 2020; Rasero 2015; Tsaousi 2015). A meta-analysis of studies from 19 countries (the majority from Europe and North America) revealed a pooled prevalence rate in hospitals of 12.8% (95% CI 11.8% to 13.9%), while the pooled rate of hospital-acquired pressure ulcers was 8.4% (95% CI 7.6 to 9.3%; Li 2020). After excluding people with stage 1 pressure ulcers (intact skin with a localized area of non-blanching erythema), the pooled hospital-acquired pressure ulcer rate was 8.0% (95% CI 7.4% to 8.6%). Lower prevalence rates are mainly reported by countries with a younger hospital population (Aljezawi 2021). In nursing homes, prevalence rates range between 3.1% and 32.9% (Carryer 2017; VanGilder 2017; Woo 2017), while a recently published study in residential hospices reported even higher prevalence rates of 34.1% (Artico 2020). Ferris 2019 examined pressure ulcers in patients receiving palliative care and found prevalence rates of 12.4%, with, however, over 50% of palliative patients in nursing homes having pressure ulcers.

A 10-year trend analysis from the USA with more than 900,000 patients showed that the overall and facility-aquired pressure ulcer prevalences decreased from 13.5% to 9.3% and from 6.2% to 3.4%, respectively, over the 10-year period (VanGilder 2017). The highest prevalence rates were detected in long-term care but also declined from 32.9% in 2006 to 28.8% in 2015. Between 2002 and 2008, the pressure ulcer prevalence rates in German long-term care facilities decreased from 12.5% to 5.0%, while non-blanchable erythema decreased from 6.6% to 3.5% (Lahmann 2010). The authors hypothesized that this decrease was due to more effective treatment strategies and better prevention.

Older patients and patients in intensive care units have a higher risk of developing a pressure ulcer (Alderden 2017; Coyer 2017; Kayser 2019; Li 2020; Zarei 2019). Other potential risk factors of pressure ulcers identified in systematic reviews are immobility, diabetes, vascular disease, perfusion issues, mechanical ventilation, surgery and impaired nutrition or malnutrition (Alderden 2017; Dube 2022). Being overweight seems to have a protective effect on the development of pressure ulcers, while underweight people have an increased risk of developing one (Alipoor 2021). A pressure ulcer has a negative impact on the quality of life of those affected. In addition to physical consequences such as pain, a pressure ulcer can negatively influence the independence and autonomy of the person affected and lead to a restriction of social participation (Burston 2022).

Pressure ulcer prevention involves a number of strategies designed to address both extrinsic factors, such as reducing the pressure duration or magnitude at the skin surface by repositioning or use of pressure-relieving cushions or mattresses (McInnes 2018), and intrinsic factors, such as increasing the ability of the patient's skin to remain intact and resist pressure damage by optimising hydration, circulation and nutrition (Liu 2017; Moore 2018; Song 2020).

Many risk assessment tools include poor nutritional status as a risk factor (e.g. Braden 1994; Gosnell 1989). There is also consensus that nutrition is an important factor, as shown by its incorporation into international guidelines, for example, the EPUAP, NPIAP and PPPIA clinical practice guideline (EPUAP, NPIAP and PPPIA 2019). They recommend the development and implementation of an individualized nutrition care plan for malnourished patients with a risk of pressure ulcers, as well as nutritional supplements for malnourished patients with a pressure injury at stage 2 or higher (EPUAP, NPIAP and PPPIA 2019; Munoz 2020).

Description of the condition

A pressure ulcer - also known as a pressure sore, decubitus ulcer or bedsore - is defined as a "localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear" (EPUAP, NPIAP and PPPIA 2019). Shear pressure occurs when layers of skin are forced to slide over one another or over deeper layers of tissue, for example, when a patient slides down the bed. Friction is also thought to contribute.Applied pressure affects cellular metabolism by decreasing or obliterating tissue circulation, resulting in insufficient blood flow to the skin and underlying tissues and causing tissue ischaemia (Agrawal 2012; EPUAP, NPIAP and PPPIA 2019).

Pressure ulcer classification systems allow a consistent description of the severity and level of tissue injury of a pressure ulcer. The words 'stage', 'grade', and 'category' may be used interchangeably to describe the levels of soft-tissue injury (EPUAP, NPIAP and PPPIA 2019). The classification includes stages 1 through to 4 and was revised in 2016 by the National Pressure Ulcer Advisory Panel (NPUAP) and defined as follows: stage 1 represents intact skin with a localized area of non-blanching erythema, stage 2 involves partial-thickness skin loss with exposed dermis, stage 3 represents full-thickness skin loss in which fat is visible in the ulcer and granulation and epibole are often present, whereas the damage in stage 4 extends to a full-thickness skin and tissue loss with exposed fascia, muscle, ligament or bone (Edsberg 2016; EPUAP, NPIAP and PPPIA 2019). Even though the classification includes a comprehensive explanation of the staging system, a pressure ulcer stage cannot always be determined exactly, for example in darkly pigmented skin or if slough or eschar obscures the extent of tissue loss. In the latter case, the pressure ulcer is referred to as an unstageable pressure injury (Edsberg 2016).

Description of the intervention

Nutritional interventions include special diets or nutritional supplementation, administered enterally or parenterally. Enteral nutrition is given via the mouth or by tube and absorbed by the digestive system. Parenteral nutrition is given via the bloodstream, for example, by means of intravenous infusion or intramuscular injection. Nutritional supplements consist of macronutrients, such as proteins, carbohydrates and fats, or micronutrients, such as vitamins and minerals, or a combination of some or all of these. Usually, combinations of micro- and macronutrients are offered in different compositions.

How the intervention might work

There is some evidence that the incidence and severity of pressure ulceration increases with poor nutrition (Alipoor 2021; Posthauer 2015). Decreased energy intake, dehydration, and a drop in serum albumin levels may decrease the tolerance of skin and underlying tissue to pressure, friction, and shearing force, thus increasing the risk of skin breakdown and reducing wound healing ability (Mueller 2001). Serum albumin is commonly used as a measure of the amount of protein available in the blood for healing. The

combination of low energy and low protein intake is often described as protein-calorie or protein-energy malnutrition. A few studies have suggested a correlation between protein-calorie malnutrition and pressure ulcers (Agarwal 2016; Cereda 2017). Evidence also shows that malnutrition increases pressure ulcer risk fourfold (Ness 2018), and that nutrition support is necessary for wound healing (Stratton 2005). Therefore, international guidelines highlight the importance of providing appropriate nutrition support for pressure ulcer prevention and treatment. For instance, even though protein is essential for maintaining skin integrity through collagen and connective tissue synthesis, adequate energy intake from carbohydrates and fat is also important to prevent the body from using amino acids in protein as an energy source (Posthauer 2015). Micronutrients, particularly antioxidants, are necessary for collagen synthesis (Posthauer 2015). However, it is unknown whether a separate supplementation or a combination of energy, protein and micronutrient supplements have an effect on pressure ulcer prevention and treatment. It is also unclear whether specific amino acids or micronutrients may provide a better effect than other amino acids or micronutrients in preventing or treating pressure ulcers. Some studies found benefits from using arginine (Liu 2017), vitamin C (Ter Riet 1995), and zinc (Song 2020), in wound healing, however, the evidence is still uncertain. Arginine is an essential amino acid that acts as a substrate for collagen synthesis and deposition, both of which are essential for maintaining skin integrity and wound healing (Desneves 2005). Arginine is consequently thought to be related to pressure ulcers. Vitamin C deficiency is connected with scurvy, which is characterized by poor wound healing and is therefore thought to be related to pressure ulcers (Ter Riet 1995). Similarly, a low serum zinc level is associated with the development of pressure ulcers as an indication of malnutrition, and, hence, zinc supplementation is thought to be related to pressure ulcer prevention and treatment (Desneves 2005). Consequently, a comparison of different types of nutritional interventions for preventing and treating pressure ulcers is essential to guide evidence-informed clinical practice.

Why it is important to do this review

The effects of nutritional interventions (e.g. special diets or nutritional supplements) in preventing and treating pressure ulcers have been examined in systematic reviews, but with conflicting results (Carryer 2017; Daher 2022; Liu 2017; Song 2020), and limitations (Yap 2021). This second update of the original systematic review first published in 2003 was required to summarize the best research available and to enable evidence-based guidance on the role of nutritional interventions in the prevention and treatment of pressure ulcers.

OBJECTIVES

To evaluate the benefits and harms of nutritional interventions (special diets, supplements) for preventing and treating pressure ulcers in people with or without existing pressure ulcers compared to standard diet or other nutritional interventions.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) of parallel or cross-over design that evaluated the effect of nutritional interventions on the prevention and treatment of pressure ulcers by measuring the incidence of new ulcers, ulcer healing rates or changes in pressure ulcer severity. We did not include quasi-randomized trials.

Types of participants

People in need of care, of any age or sex, with or without existing pressure ulcers, in any care setting, irrespective of primary diagnoses. For the purpose of this review, a pressure ulcer was defined as an area of localized damage to the skin and underlying tissue caused by pressure, shear, friction or a combination of these. If only a portion of study participants were eligible for inclusion, we included them if separate data were available. If not, we contacted the study authors to obtain the data. If separate use of the data was not possible, we excluded the study.

Types of interventions

We included clearly described nutritional interventions (special diets or supplements; enteral or parenteral nutrition). Nutritional interventions of interest are supplemented energy, protein, fat or micronutrients, or disease-specific diets. Comparisons between nutritional supplements plus standard diet versus standard diet alone were eligible.

We excluded studies that provided nutrition supplementation as part of a multifactorial intervention (e.g. interventions with education and physical activity) because the effect of the nutritional supplement cannot be inferred from these studies.

There were no selection criteria regarding the duration of the intervention. In terms of the recommended duration of intervention, the clinical guideline suggests that the duration of intervention in pressure ulcer treatment should be at least four weeks to allow for complete pressure ulcer healing (Munoz 2020). There is no suggestion for the duration of intervention in pressure ulcer prevention because these interventions aim to prevent malnutrition or improve malnutrition status by providing at least 80% of daily estimated energy and protein needs (Munoz 2020).

Types of outcome measures

We considered the primary and secondary outcomes described below. The systematic recording of pressure ulcers (new ulcers, development of existing ones, healing process) was an inclusion criterion for the review. Studies could assess the healing process using a validated assessment tool for measuring pressure ulcer healing, such as the Pressure Sore Status Tool (PSST), the Pressure Ulcer Scale for Healing (PUSH) or the DESIGN/R-DESIGN tool (Smet 2021).

If studies reported pressure ulcers only as adverse events of a nutritional intervention, pressure ulcers had to be reported in the baseline characteristics to assess whether new pressure ulcers had developed; if not, we excluded the study.

Primary outcomes

We reported outcome measures at the last time point available (assumed to be length of follow-up if not specified otherwise).

Prevention studies:

- incidence of pressure ulcers (the proportion of people who developed any new pressure ulcer of any stage).

Treatment studies:

- time to complete healing;
- healed pressure ulcers;
- change in pressure ulcer area or depth or volume;
- progress of healing (measured by any of the validated assessment tools described above);
- rate of pressure ulcer healing.

Secondary outcomes

Prevention studies:

- time to pressure ulcer development.

Prevention and treatment studies:

- acceptability of nutritional supplements;
- side effects (e.g. gastrointestinal side effects: diarrhoea, constipation, dyspepsia, nausea, vomiting, or headache);
- costs;
- health-related quality of life (measured by means of a validated instrument like the generic EQ-5D-5L (Feng 2021), or the disease-specific PU-QOL-P (Rutherford 2018).

We expected studies to conduct multiple measurements or observations of a single outcome in the same participants (repeated measurements) to build the process. If this was the case, we only extracted and analyzed the data point for the longest available follow-up. The timing of outcome assessment was specified as time until discharge for studies in hospitals and as the intervention duration in other settings.

The nature of the primary outcomes for prevention studies makes it difficult to determine when to expect results. In many of these studies, pressure ulcers are a complication; and in prevention studies, it is hoped that no event will occur. It cannot be predicted when to expect an outcome in these studies.

The time to complete healing depends on the size and severity of the pressure ulcer, it is therefore not possible to specify required periods.

Secondary outcomes were collected during the course of treatment and extracted and analyzed as reported.

Search methods for identification of studies

In May 2022 we searched the electronic databases below. We also searched clinical trials registries for ongoing and unpublished studies and scanned reference lists of relevant included studies as well as reviews, meta-analyses, and health technology reports to identify additional studies. There were no restrictions with respect to language, date of publication, or study setting.

Electronic searches

We searched the following electronic databases to identify reports of relevant clinical trials:

- Cochrane Wounds Specialised Register (searched 31 May 2022);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 4) in the Cochrane Library (searched 31 May 2022);
- MEDLINE Ovid including In-Process & Other Non-Indexed Citations (1946 to 31 May 2022);
- Embase Ovid (1974 to 31 May 2022);
- CINAHL Plus EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1937 to 31 May 2022);
- Database of Abstracts of Reviews of Effects (DARE) Centre for Reviews and Dissemination (CRD) (1994 to March 2015);
- Health Technology Assessment Database (HTA) Centre for Reviews and Dissemination (CRD) (1996 to March 2018);
- NHS Economic Evaluation Database (NHS EED) Centre for Reviews and Dissemination (CRD) (1994 to March 2015);
- International Network of Agencies for Health Technology Assessment (INAHTA) 1996 to 31 May 2022).

We provide the search strategies for the Cochrane Wounds Specialised Register, CENTRAL, MEDLINE Ovid, Embase Ovid, and CINAHL Plus EBSCO in Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5. In MEDLINE Ovid, we combined the subject-specific strategy with the sensitivity-maximizing version of the Cochrane highly sensitive search strategy for identifying randomized trials (2008 revision) (Lefebvre 2022). We combined the Embase Ovid search with the Embase Ovid filter developed by Cochrane UK (Lefebvre 2022). We combined the CINAHL Plus EBSCO search with the trial filter developed by Glanville 2019. There were no restrictions with respect to language, date of publication, or study setting.

We combined MEDLINE Ovid and Embase Ovid searches with adapted filters developed by the Centre for Reviews and Dissemination for the identification of economic studies (CRD 2013).

We also searched the following clinical trials registries:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (searched 31 May 2022);
- World Health Organization (WHO) International Clinical Trials Registry Platform (https://trialsearch.who.int/) (searched 31 May 2022).

Search strategies for clinical trials registries can be found in Appendix 6; Appendix 7.

Details of the search strategies used for the previous version of the review are given in Appendix 8.

Searching other resources

Searching reference lists of included studies and relevant reviews

In order to identify other potentially eligible studies or ancillary publications, we searched the reference lists of retrieved included studies, as well as of relevant systematic reviews, meta-analyses and health technology assessment reports.

Adverse effects

We did not perform a separate search for adverse effects of interventions used, we considered adverse effects described in included studies only.

Data collection and analysis

We carried out data collection and analysis as described in the former version of this review (Langer 2014), and updated the methods as appropriate using the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a).

We used Covidence for title/abstract screening, full-text screening, and data extraction.

Selection of studies

Two review authors independently assessed results from the search for potential eligibility, and any disagreement was resolved by discussion with a third review author. We retrieved potentially relevant studies in full, and two review authors decided, independently, whether these studies met the inclusion criteria.

Data extraction and management

We entered references identified from searches into a bibliographic software package. We extracted details of eligible studies and summarized them using a data extraction sheet. The data extraction sheet was based on the one used for the previous version of this review. Two review authors, independently, extracted some studies and completed the sheet; after discussion among the research team, we agreed to use this extraction sheet. Two review authors simultaneously and independently extracted data. Any disagreements were resolved by discussion. We included studies published in duplicate only once, except when multiple publications provided additional data. If support was needed for other languages, we contacted experienced colleagues who were proficient in the required language and extracted the data together with these colleagues.

We extracted the key characteristics of the studies, such as study design, setting, sample size, population, inclusion and exclusion criteria, and how outcomes were defined or collected in the studies. In addition, we collected baseline information on prognostic factors or effect modifiers that result in group differences. For the purpose of this review, this included characteristics of existing pressure ulcers (e.g. stage, multiple pressure ulcers), nutritional status, differences in the consumption of energy, proteins, or other nutrients, and possible differences in the numbers of long-term healthcare staff.

To describe and categorize the manifold interventions, we extracted:

- type of diet/supplementation;
- macronutrients and micronutrients;
- additional energy;
- amount of supplementation;
- mode of feeding;
- intervention period.

Assessment of risk of bias in included studies

Two of the four review authors (CSW, DS, AF, GL) each independently assessed the risk of bias for each included study using the Risk of Bias 2 (RoB 2) tool in May 2022 (Sterne 2019). We resolved all disagreements by discussion among the review authors. Concerning studies with non-standard designs, such as cross-over trials and cluster-randomized trials, we used the special variants of the RoB 2 tool for cross-over trials and cluster-randomized trials. However, the latter was not required. We used the Risk-Of-Bias VISualization (robvis) tool for a comprehensive presentation of the RoB 2 appraisals in figures (McGuinness 2020).

We assessed risk of bias for each study that addressed one of our primary outcomes. For the prevention studies, this was the incidence of new pressure ulcers. With respect to the treatment studies, we specified the outcome that validly represented pressure ulcer development or healing according to our defined possible outcomes: size and depth of pressure ulcers, rate of pressure ulcer healing, time to complete healing, and number of people with healed pressure ulcers. The timing of outcome assessment was time until discharge for studies in hospitals, otherwise the duration of the intervention as stated in the study. Our primary intention was to assess the effects of assignment, rather than adherence, to treatment.

We assessed five risk of bias domains, namely: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result - plus ‘overall risk of bias’. We used the signaling questions for each domain, which can be answered with 'yes', 'probably yes', 'probably no', 'no' and 'no information', with a suggested algorithm for reaching judgement via an MS Excel macro (MS Excel). We included text excerpts alongside the judgements in the MS Excel file to provide supporting information for our decisions. The judgements resulted in 'low risk', 'some concerns', or 'high risk' for each domain and for overall risk of bias.

We presented the risk of bias assessment using risk of bias summary figures, which show all judgements in a cross-tabulation of studies by entry (Figure 1; Figure 2; Figure 3). This display of internal validity indicates the weight the reader may give to the results of each study, which is why the RoB 2 assessments are also shown in the forest plots.

Figure 1. Risk of bias assessment traffic light plot for individual randomized studies

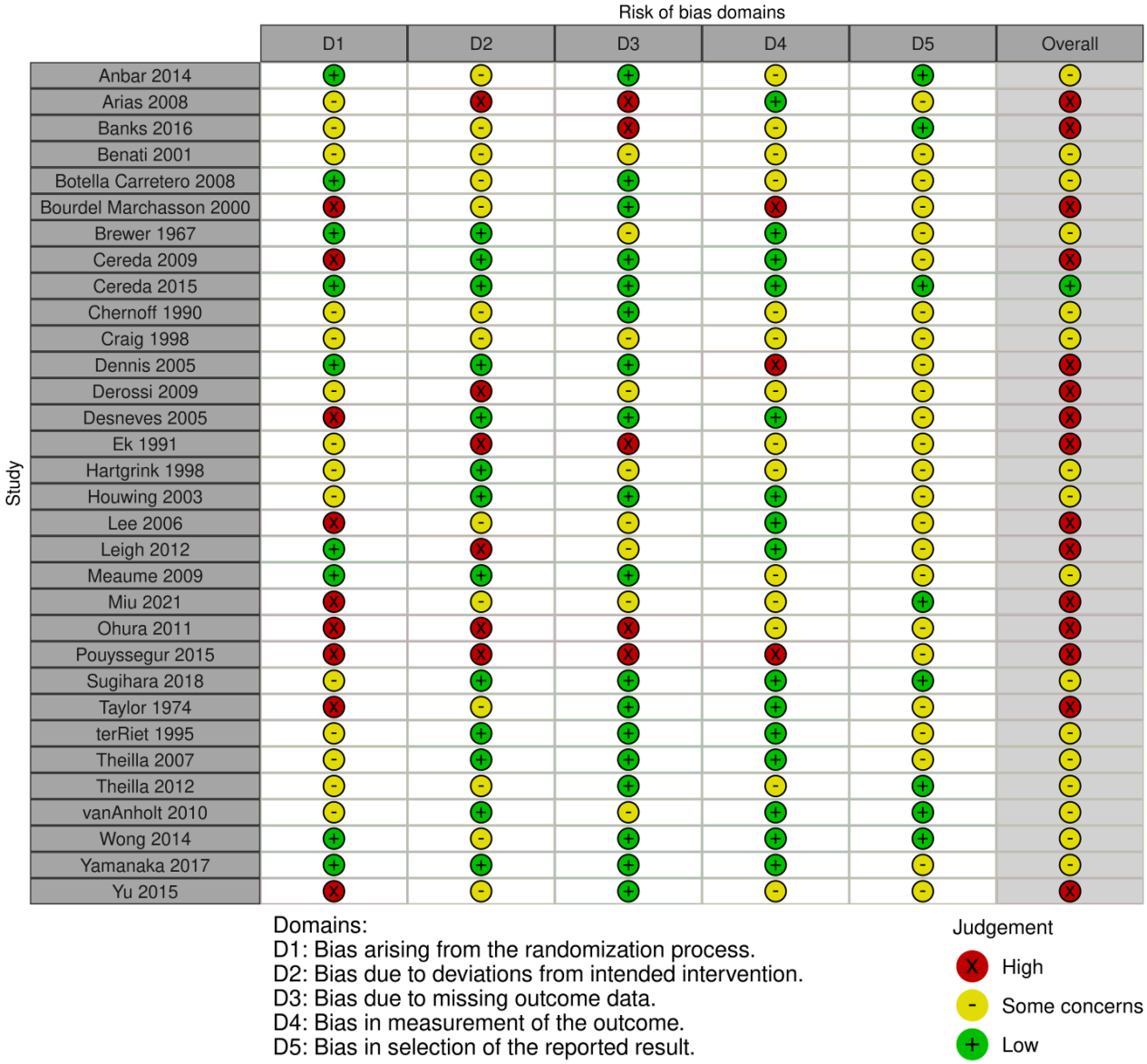


Figure 2. Risk of bias summary plot in percentages for individual randomized studies. This review includes 33 studies.

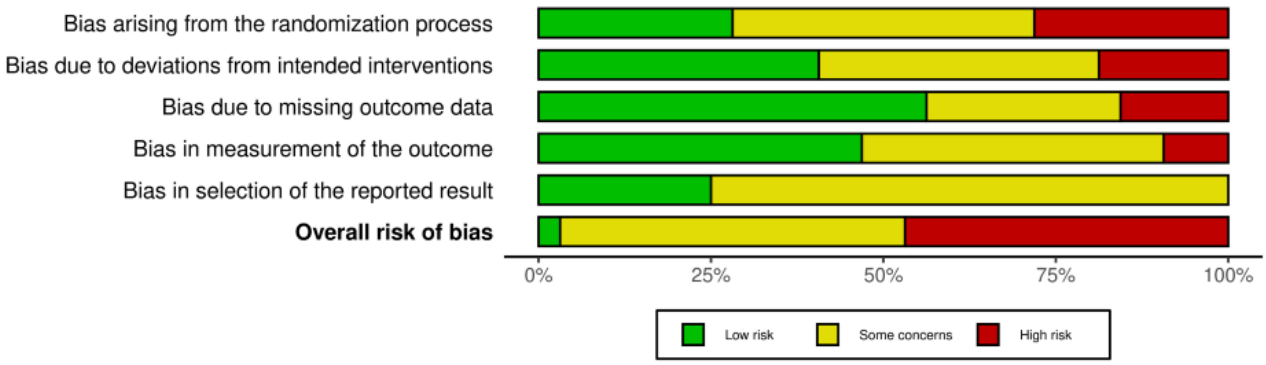
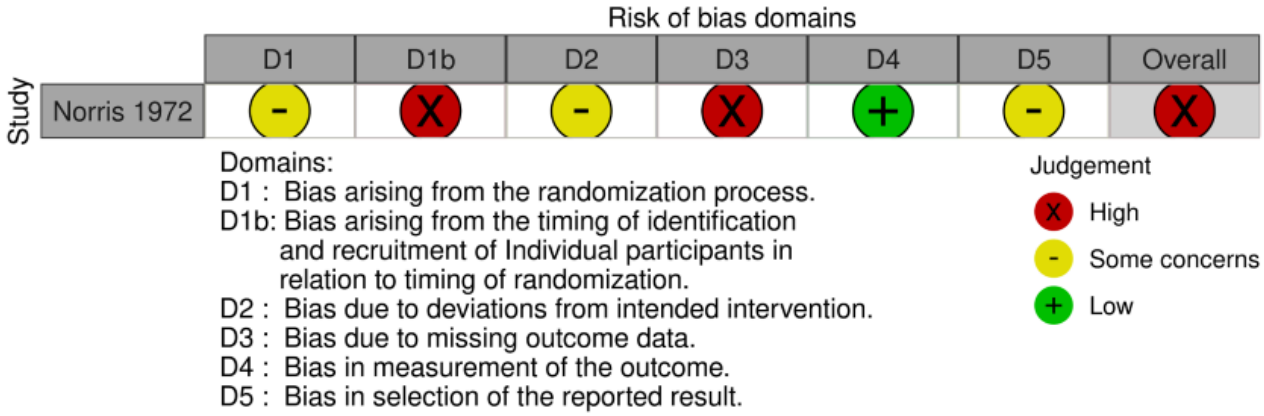


Figure 3. Risk of bias traffic light plot for cross-over studies



Measures of treatment effect

For dichotomous outcomes, we calculated the risk ratio (RR) with 95% confidence intervals (CI). For continuous outcomes, we used the mean difference (MD) with 95% CIs in cases where studies reported the same or similar assessment scales. If a median was reported with minimum, maximum and interquartile ranges, we used these values to estimate the sample mean and standard deviation (SD; Shi 2020). Wherever studies reported different assessment scales for the same outcome, we used the standardized mean difference (SMD) with 95% CIs. We analyzed outcomes with time-to-event data using the methods of survival analysis, and expressed the intervention effect as a hazard ratio (HR).

Unit of analysis issues

Where possible, we always considered individual participants, regardless of whether they had multiple pressure ulcers. If studies reported the number of pressure ulcers, we stated it explicitly.

For cross-over trials, we intended to consider only outcome data regarding the first intervention phase (i.e. prior to cross-over) as eligible.

If a future update identifies cluster-RCTs, we plan to incorporate them according to the advice in section 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022b).

To include a study with more than one intervention group, we combined multiple groups that were eligible as the experimental or comparator intervention to create a single pair-wise comparison.

We expected studies to conduct multiple measurements or observations of a single outcome in the same participants (repeated measurements). If this was the case, we only extracted and analyzed the data point for the longest available follow-up.

Dealing with missing data

Due to often small sample sizes and mostly low study quality, it did not seem appropriate to impute missing data.

Assessment of heterogeneity

If it was possible to pool data from separate studies, we assessed between-study heterogeneity with both the Chi^2 test and the I^2 statistic. We regarded I^2 statistic value greater than 60% and Chi^2 test with a significance level of $P < 0.10$ as indicative of serious heterogeneity (Deeks 2022). We also considered clinical heterogeneity.

Assessment of reporting biases

For comparisons with more than seven included studies, we created funnel plots and conducted Egger's regression tests to investigate a possible publication bias (Egger 1997).

Data synthesis

We included all eligible studies in the primary analysis, irrespective of the result of the risk of bias assessment. We considered a random-effects model appropriate for the meta-analyses of nutritional interventions because the intervention effects of the respective nutritional interventions varied depending on the participants' malnutrition status, the dose and duration of nutritional supplementation, and the type of nutritional intervention in the control group, and also differed within the included studies.

We planned the following comparisons:

- supplements/diet in addition to a standard diet compared with standard diet alone;
- comparisons between different types of supplement/diets.

Subgroup analysis and investigation of heterogeneity

We considered the following subgroup analyses regarding the primary outcome (pressure ulcer incidence and ulcer healing):

- characteristics of the setting (e.g. hospital inpatients versus outpatients);
- method of feeding (e.g. enteral versus parenteral feeding, if the study conditions allowed it);
- patient characteristics (e.g. people with pre-existing malnutrition versus people without malnutrition).

The different prevalence rates in the various settings (see Background), suggest that differences may exist with respect to the individuals' risks and regarding the treatment. Therefore, it seems more appropriate to consider these separately, to better assess the impact of the nutritional intervention. Malnutrition is both a risk factor for pressure ulcer development and an important factor in wound healing (see Background). For this reason, the results of malnourished and non-malnourished people should be considered separately.

Sensitivity analysis

We planned to carry out sensitivity analyses to determine whether the findings are robust with regard to the decisions made in the course of identifying, screening and analyzing the trials. We planned to perform sensitivity analyses for the following factors, if the appropriate data were available:

- impact of single outlying studies on the results of a meta-analysis: exclusion of single outlying studies to evaluate the impact;
- risk of bias of included studies: exclusion of studies with a high risk of overall bias for the result.

If any of these investigations found a difference in the size of the effect or heterogeneity, we intended to mention this in the 'Effects of interventions' section. However, there were insufficient studies and data meeting these criteria, and these analyses were therefore not required. We have a maximum of four studies in our meta-analysis and only one outcome of a single study without concerns in the risk of bias assessment. We did not report these analyses because we did not want to put too much strain on the data.

Summary of findings and assessment of the certainty of the evidence

We created summary of findings tables for the following outcomes (see Primary outcomes; Secondary outcomes).

- The proportion of participants developing new pressure ulcers (incidence), time to pressure ulcer development (for prevention studies)
- Time to complete healing, healed pressure ulcers, change in area or depth or volume of pressure ulcers (for treatment studies)
- Acceptability of supplements
- Side effects
- Costs
- Health-related quality of life

We created summary of findings tables for the corresponding comparisons.

- Energy, protein and micronutrients versus standard diet for the prevention of pressure ulcers
- Protein, arginine, zinc and antioxidants versus placebo for the prevention of pressure ulcers
- L-carnitine, L-leucine, calcium, magnesium, vitamin D versus standard diet for the prevention of pressure ulcers
- EPA, GLA and antioxidants versus standard diet for the prevention of pressure ulcers
- Protein versus standard diet for the prevention of pressure ulcers
- Disease-specific supplement versus standard high-carbohydrate formula for the prevention of pressure ulcers
- Energy, protein and micronutrients versus standard diet for treating pressure ulcers
- Protein, arginine, zinc and antioxidants versus standard diet or placebo for treating pressure ulcers
- Arginine and micronutrients versus standard diet or placebo for treating pressure ulcers
- Different doses of arginine for treating pressure ulcers
- EPA, GLA and antioxidants versus standard diet for treating pressure ulcers
- Protein versus standard diet for treating pressure ulcers
- Collagen versus standard diet or placebo for treating pressure ulcers
- Specialized amino acid mixture (arginine-enriched) versus standard diet or placebo for treating pressure ulcers
- Ornithine alpha-ketoglutarate versus placebo for treating pressure ulcers
- Vitamin C versus placebo for treating pressure ulcers
- Zinc sulphate versus placebo for treating pressure ulcers

We used the GRADE domains of bias risk, inconsistency, imprecision, indirectness, and publication/dissemination bias for downgrading. We used the methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022,), using GRADEpro

GDT software. One review author (LS) judged the certainty of the evidence and a second review author (DS) checked the judgements. Disagreements were resolved by discussion. We clarified certainty of evidence ratings in footnotes in the summary of findings tables. If not stated otherwise, the baseline risk used to calculate absolute effects is based on the risk in the control group (i.e. placebo or treatment-as-usual group). The results are expressed by means of one of four certainty levels (high, moderate, low or very low).

RESULTS

Description of studies

See Included studies; Excluded studies; Studies awaiting classification and Ongoing studies.

Results of the search

Our search strategy in 2003 identified 942 articles from online databases (MEDLINE (PubMed), CINAHL and CENTRAL). A further 13 articles were retrieved by handsearching; 17 were referred to us by experts and manufacturers; and a further 23 were found by scanning bibliographies of relevant papers. In addition, Cochrane Wounds identified a further nine articles. After merging the results and removing duplicates, 912 citations were left and were reviewed independently. Two of the review authors had an initial overall agreement of 99% (904/912) and identified 16 studies related to potentially relevant trials, which were then retrieved in full text. Disagreements were resolved by discussion and the rating of the third author. Eight trials met the inclusion criteria for the original version of this review.

Our search strategy in 2011 identified 175 articles from online databases (MEDLINE (PubMed), EMBASE, CINAHL and CENTRAL), 19 by scanning bibliographies of relevant papers and seven by searching registration databases. In addition, Cochrane Wounds identified a further six articles. After merging the results and removing duplicates, 197 citations were left and were reviewed independently. The two review authors had an initial overall agreement of 98% (192/197) and identified 22 studies related to potentially relevant trials, which were then retrieved in full text (see Figure 4). Disagreements were resolved by discussion. Fifteen trials met the inclusion criteria, increasing the total number of included studies to 23 (27 citations).

Figure 4. Study flow diagram

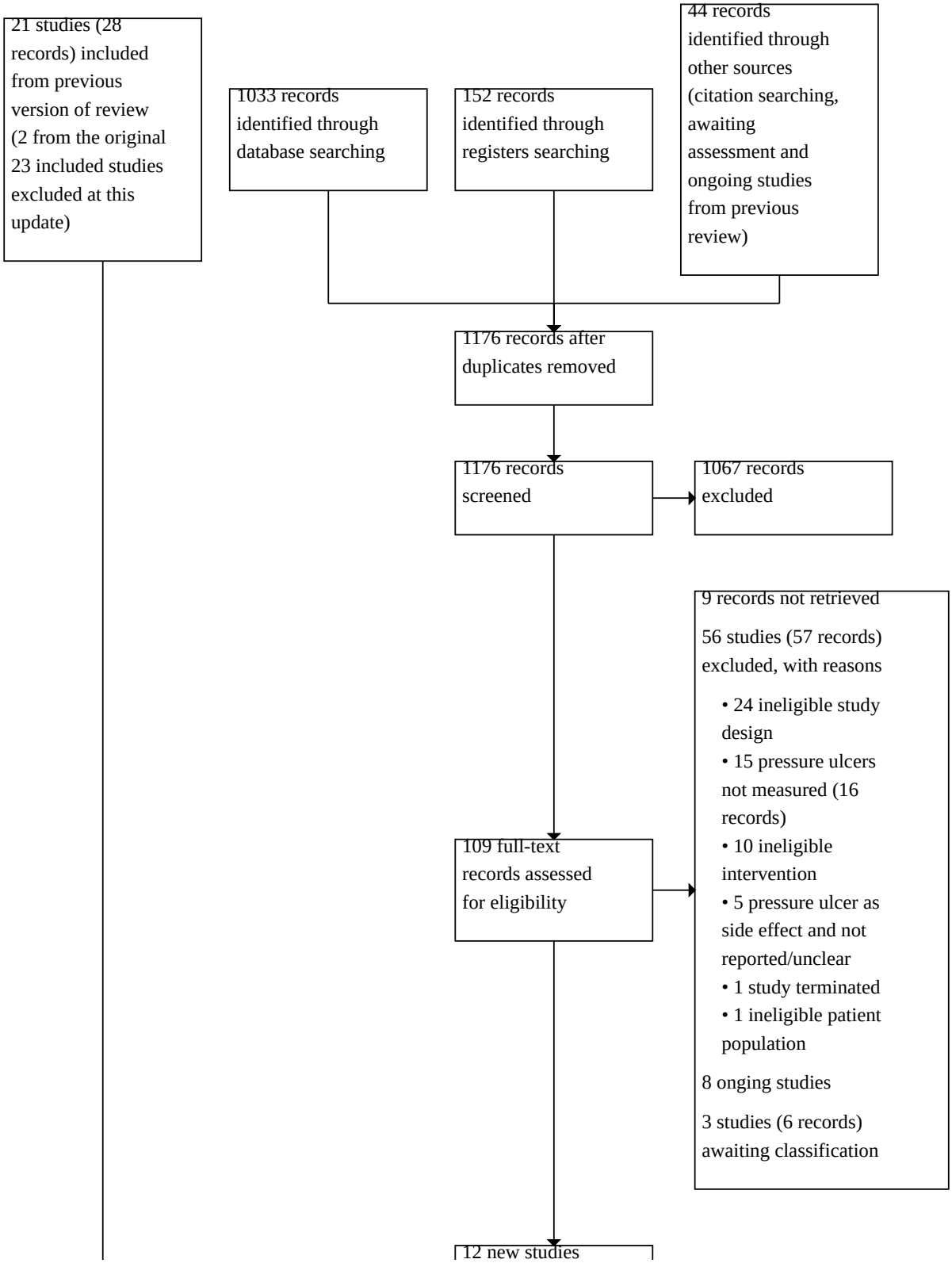
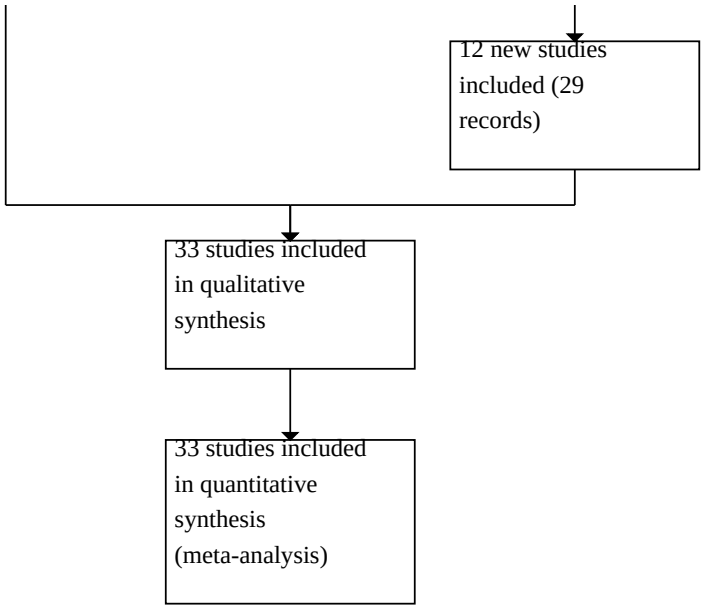


Figure 4. (Continued)



For the second update in 2022, we identified 1229 records. The electronic search generated 1033 records from databases (Cochrane Wounds Specialised Register, CENTRAL, MEDLINE, Embase, CINAHL, DARE, HTA, NHS EED, INAHATA) and 152 from trials registries. We identified a further 30 records by scanning bibliographies of relevant papers, and added 14 records from the previous version of the review that had been classified as awaiting assessment or ongoing records at that time. We removed 33 duplicate records and 20 identified records from the previous version of the review. Of the 1176 records that were screened independently, we excluded 1067. Of the remaining 109 records, we were unable to retrieve nine. Most of these were older study protocols or conference abstracts for which we had either not received a response from the authors or could not find contact details. We excluded 57 records (56 studies) with reasons and categorized 11 studies as awaiting classification or ongoing. Following full-text screening, we considered 12 new studies (from 29 records) to be eligible for inclusion in this review update. Of the 23 studies included in the previous version of the review, two were excluded by consensus: one because pressure ulcers were only mentioned as side effects, and it was unclear if these were new-onset pressure ulcers (Delmi 1990), and one because the intervention was multifactorial rather than nutritional (Olofsson 2007). The total number of included studies in this review is 33 from 57 reports (we found and added additional reports for two studies in the previous review). See Figure 4.

Included studies

Thirty-three RCTs are now included in the review (see Included studies); comprising 21 RCTs from the previous version of the review and 12 newly included RCTs.

Types of studies

All included studies were parallel-group RCTs, except one, which was a cross-over trial with participants being their own controls (Norris 1971). Eleven studies were multi-centre trials (Bourdel Marchasson 2000; Cereda 2009; Cereda 2015; Craig 1998; Dennis 2005; Houwing 2003; Lee 2006; Meaume 2009; Ohura 2011; Ter Riet 1995; Van Anholt 2010), with three studies being carried out cross-nationally (Dennis 2005; ; Meaume 2009; Van Anholt 2010).

Twenty-two studies were conducted as treatment studies where the included participants already had pressure ulcers (Banks 2016; Benati 2001; Brewer 1967; Cereda 2009; Cereda 2015; Chernoff 1990; Desneves 2005; Lee 2006; Leigh 2012; Meaume 2009; Miu 2021; Norris 1971; Ohura 2011; Pouyssegur 2015; Sugihara 2018; Taylor 1974; Ter Riet 1995; Theilla 2012; Van Anholt 2010; Wong 2014; Yamanaka 2017; Yu 2015), and nine as pressure ulcer prevention studies (Anbar 2014; Arias 2008; Botella Carretero 2008; Bourdel Marchasson 2000; Craig 1998; Dennis 2005; Derossi 2009; Hartgrink 1998; Houwing 2003). Two studies focused both on the prevention and treatment of pressure ulcers (Ek 1991; Theilla 2007).

Types of settings

Twenty-three of the 33 studies were carried out in hospitals (Anbar 2014; Arias 2008; Banks 2016; Benati 2001; Botella Carretero 2008; Bourdel Marchasson 2000; Dennis 2005; Derossi 2009; Desneves 2005; Hartgrink 1998; Houwing 2003; Leigh 2012; Meaume 2009; Miu 2021; Norris 1971; Ohura 2011; Sugihara 2018; Taylor 1974; Theilla 2007; Theilla 2012; Wong 2014; Yamanaka 2017; Yu 2015), five in long-term care facilities (Cereda 2009; Cereda 2015; Craig 1998; Lee 2006; Pouyssegur 2015), two in hospitals and long term-care facilities (Ter Riet 1995; Van Anholt 2010), and one in a long-term care unit of a university hospital (Ek 1991). Two studies did not clearly describe the type of setting (Brewer 1967; Chernoff 1990). The type of hospital department varied widely and ranged from intensive care units (Theilla 2007; Theilla 2012), to departments for geriatric medicine (Anbar 2014; Benati 2001; Bourdel Marchasson 2000; Meaume 2009).

Most studies were conducted in Europe (Benati 2001; Botella Carretero 2008; Bourdel Marchasson 2000; Cereda 2009; Cereda 2015; Derossi 2009; Ek 1991; Hartgrink 1998; Houwing 2003; Meaume 2009; Pouyssegur 2015; Taylor 1974; Ter Riet 1995), or Asia (Anbar 2014; Miu 2021; Ohura 2011; Sugihara 2018; Theilla 2007; Theilla 2012; Wong 2014; Yamanaka 2017; Yu 2015). Four studies were carried out in the USA (Chernoff 1990; Craig 1998; Lee 2006; Norris 1971), three in Australia (Banks 2016; Desneves 2005; Leigh 2012), and one in Uruguay (Arias 2008). Two studies were cross-continental trials (Dennis 2005; Van Anholt 2010). It is unclear in which country Brewer 1967 was carried out.

Types of participants

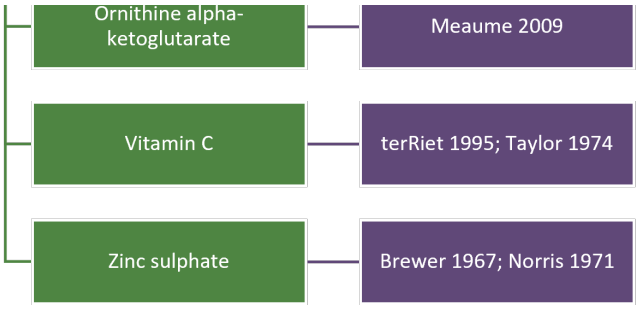
Most of the studies included in the review were small. The median sample size was 76 participants, with a range from 12 (Chernoff 1990), to 4023 participants (Dennis 2005). Four studies had a sample size of more than 500 participants (Arias 2008; Bourdel Marchasson 2000; Dennis 2005; Ek 1991). The majority of the studies included geriatric patients with a mean age over 80 years (Anbar 2014; Botella Carretero 2008; Bourdel Marchasson 2000; Cereda 2009; Cereda 2015; Craig 1998; Derossi 2009; Ek 1991; Hartgrink 1998; Houwing 2003; Meaume 2009; Miu 2021; Ohura 2011; Pouyssegur 2015), while three studies investigated participants below a mean age of 60 years (Norris 1971; Sugihara 2018; Theilla 2012). Four studies did not state the mean age (Benati 2001; Brewer 1967; Lee 2006; Ter Riet 1995). In terms of gender ratio, the proportion of women was higher than men in 18 studies (Anbar 2014; Botella Carretero 2008; Bourdel Marchasson 2000; Cereda 2009; Cereda 2015; Chernoff 1990; Derossi 2009; Ek 1991; Hartgrink 1998; Houwing 2003; Meaume 2009; Miu 2021; Ohura 2011; Pouyssegur 2015; Taylor 1974; Van Anholt 2010; Wong 2014; Yamanaka 2017), with the highest proportion of women being 87.6% in Hartgrink 1998. The highest proportion of men was observed in the study by Theilla 2012, with 67.5% men. Four studies provided no information on gender distribution (Brewer 1967; Craig 1998; Lee 2006; Ter Riet 1995). Three studies specifically recruited people with hip fractures (Derossi 2009; Hartgrink 1998; Houwing 2003). Other patient populations included stroke patients (Dennis 2005), people with spinal cord injury (Brewer 1967), and residents with type II diabetes (Craig 1998). In Wong 2014, about a quarter of the participants were affected by type II diabetes. Three studies provided information on a possible dementia diagnosis, which was present in 6% (Desneves 2005), 36 % (Ohura 2011), and 53% (Cereda 2015), of the participants in these studies. The majority of studies that assessed nutritional status included or did not explicitly exclude people with malnutrition. (Anbar 2014; Arias 2008; Banks 2016; Botella Carretero 2008; Cereda 2009; Cereda 2015; Dennis 2005; Derossi 2009; Desneves 2005; Ek 1991; Houwing 2003; Lee 2006; Leigh 2012; Meaume 2009; Miu 2021; Ohura 2011; Pouyssegur 2015; Ter Riet 1995; Theilla 2007; Theilla 2012; Wong 2014; Yamanaka 2017). Only two studies definitively excluded malnourished people (Sugihara 2018; Van Anholt 2010), although Van Anholt 2010 included people at risk of malnutrition (23.3% of participants were at risk in this study). Botella Carretero 2008 excluded patients with moderate or severe malnutrition. Malnutrition was defined in different ways and assessed with different instruments: the Mini Nutritional Assessment (MNA; Anbar 2014; Meaume 2009; Pouyssegur 2015), the Subjective Global Assessment (SGA; Arias 2008; Banks 2016; Wong 2014), the Geriatric Nutritional Risk Index (Cereda 2009), weight loss and low serum albumin concentrations (Botella Carretero 2008), clinical impression, low albumin concentration or low arm fat (Ter Riet 1995), low Body Mass Index (BMI; Cereda 2015), and without specifying an instrument (Dennis 2005; Ek 1991). In these studies, the proportion of malnourished people ranged between 8% (Dennis 2005), and 100% (Cereda 2009; Pouyssegur 2015). In Arias 2008, 75% of the participants were at risk of being malnourished and 25% were malnourished. Several studies reported on the average BMI of the participants (Anbar 2014; Banks 2016; Botella Carretero 2008; Cereda 2009; Cereda 2015; Derossi 2009; Desneves 2005; Houwing 2003; Lee 2006; Leigh 2012; Meaume 2009; Miu 2021; Ohura 2011; Pouyssegur 2015; Sugihara 2018; Ter Riet 1995; Theilla 2007; Theilla 2012; Yamanaka 2017, which ranged from 17.1 (control group in Ohura 2011) to 32.1 (control group in Theilla 2012). No information on either nutritional status or BMI was available in nine studies (Benati 2001; Bourdel Marchasson 2000; Brewer 1967; Chernoff 1990; Craig 1998; Hartgrink 1998; Norris 1971; Taylor 1974; Yu 2015).

Types of interventions

All included studies investigated nutritional supplements, while no study investigated a specific diet to prevent or treat pressure ulcers. The nutritional supplements in the included trials were quite heterogeneous, containing different compositions and different doses of micronutrients, macronutrients and other substances. An overview is provided in Figure 5. We divided pressure ulcer prevention studies into six types of interventions based on the enriched nutrients in the supplements.

Figure 5. Overview of interventions

Figure 5. (Continued)



- Energy, protein and micronutrients (3 studies: Arias 2008; Bourdel Marchasson 2000; Ek 1991);
- Protein, arginine, zinc and antioxidants (1 study: Houwing 2003);
- L-carnitine, L-leucine, calcium, magnesium and vitamin D (1 study: Derossi 2009);
- EPA, GLA and antioxidants (1 study: Theilla 2007);
- Protein (4 studies: Anbar 2014; Botella Carretero 2008; Dennis 2005; Hartgrink 1998); and
- Disease-specific (Craig 1998).

We divided studies that focused on the treatment of pressure ulcers into 11 different interventions, depending on the enriched nutrients of the administered supplements.

- Energy, protein and micronutrients (3 studies: Ek 1991; Ohura 2011; Yu 2015);
- Protein, arginine, zinc and antioxidants (4 studies: Benati 2001; Cereda 2009; Desneves 2005; Van Anholt 2010);
- Arginine and micronutrients (3 studies: Banks 2016; Cereda 2015; Yamanaka 2017);
- Different doses of arginine (1 study: Leigh 2012);
- EPA, GLA and antioxidants (2 studies: Theilla 2007; Theilla 2012);
- Protein (4 studies: Benati 2001; Chernoff 1990; Desneves 2005; Pouyssegur 2015);
- Collagen (3 studies: Lee 2006; Sugihara 2018; Yamanaka 2017);
- A specialised amino acid mixture enriched with arginine (2 studies: Miu 2021; Wong 2014);
- Ornithine alpha-ketoglutarate (1 study: Meaume 2009);
- Vitamin C (2 studies: Taylor 1974; Ter Riet 1995); and
- Zinc sulphate (2 studies: Brewer 1967; Norris 1971).

Five studies had three study arms and compared the nutritional supplement, next to a standard diet or placebo, with another kind of supplement like a protein supplement (Benati 2001; Botella Carretero 2008; Desneves 2005; Sugihara 2018; Yamanaka 2017). The majority of the control groups (n = 21) received a standard diet (Anbar 2014; Arias 2008; Banks 2016; Benati 2001; Botella Carretero 2008; Bourdel Marchasson 2000; Cereda 2009; Chernoff 1990; Craig 1998; Dennis 2005; Derossi 2009; Desneves 2005; Ek 1991; Hartgrink 1998; Miu 2021; Ohura 2011; Pouyssegur 2015; Theilla 2007; Theilla 2012; Yamanaka 2017; Yu 2015), 11 received a placebo supplement (Brewer 1967; Cereda 2015; Houwing 2003; Lee 2006; Meaume 2009; Norris 1971; Sugihara 2018; Taylor 1974; Ter Riet 1995; Van Anholt 2010; Wong 2014), and one received another kind of nutritional supplement at a lower dose (Leigh 2012).

All studies administered the nutritional supplement enterally. Four studies administered the enteral nutrition or supplement by nasogastric tube (Chernoff 1990; Craig 1998; Hartgrink 1998; Ohura 2011). Three studies provided the nutrition both by tube and orally (Banks 2016; Wong 2014; Yamanaka 2017).

Types of outcomes

Prevention

Eleven studies reported pressure ulcer incidence (Anbar 2014; Arias 2008; Botella Carretero 2008; Bourdel Marchasson 2000; Craig 1998; Dennis 2005; Derossi 2009; Ek 1991; Hartgrink 1998; Houwing 2003; Theilla 2007). Five studies considered pressure ulcer incidence as an in-hospital, postoperative or fracture-related complication (Anbar 2014; Arias 2008; Botella Carretero 2008; Dennis 2005; Derossi 2009). In addition to pressure ulcer incidence, Botella Carretero 2008 examined gastrointestinal side effects and adherence to the oral nutritional supplement by calculating the mean investigated amount of the prescribed supplement. Two studies investigated pressure ulcer incidence as well as outcomes related to pressure ulcer healing of existing ulcers (Ek 1991; Theilla 2007).

Treatment

Twenty-four studies investigated the healing of existing pressure ulcers (Banks 2016; Benati 2001; Brewer 1967; Cereda 2009; Cereda 2015; Chernoff 1990; Desneves 2005; Ek 1991; Lee 2006; Leigh 2012; Meaume 2009; Miu 2021; Norris 1971; Ohura 2011; Pouyssegur 2015; Sugihara 2018; Taylor 1974; Ter Riet 1995; Theilla 2007; Theilla 2012; Van Anholt 2010; Wong 2014; Yamanaka 2017; Yu 2015). Ten studies assessed complete healing or time to complete healing (Brewer 1967; Cereda 2009; Cereda 2015; Chernoff 1990; Ek 1991; Leigh 2012; Ohura 2011; Taylor 1974; Theilla 2007; Yu 2015). The included studies used three different validated scores to evaluate wound characteristics: the PUSH score (Cereda 2009; Desneves 2005; Lee 2006; Leigh 2012; Miu 2021; Sugihara 2018; Theilla 2012; Van Anholt 2010; Wong 2014), the PSST score (Benati 2001; Sugihara 2018), and the DESIGN-R score (Yamanaka 2017). Other studies considered change in pressure ulcer prevalence (Pouyssegur 2015), or reduction in pressure ulcer size or area (Banks 2016; Cereda 2009; Cereda 2015; Chernoff 1990; Meaume 2009; Miu 2021; Norris 1971; Sugihara 2018; Taylor 1974; Ter Riet 1995; Van Anholt 2010; Wong 2014; Yamanaka 2017). Nine studies noted gastrointestinal adverse effects or side effects, like constipation or dyspepsia, with respect to the supplements (Banks 2016; Cereda 2015; Leigh 2012; Meaume 2009; Miu 2021; Ohura 2011; Pouyssegur 2015; Van Anholt 2010; Yamanaka 2017). Two studies described costs of care (Cereda 2015;

Pouyssegur 2015), and two described acceptance of the product (Banks 2016; Leigh 2012). No studies assessed quality of life.

Funding sources

Fifteen studies were supported by pharmaceutical companies, either by grants, personnel fees, or provision of the supplements (Cereda 2009; Cereda 2015; Craig 1998; Hartgrink 1998; Houwing 2003; Lee 2006; Meaume 2009; Norris 1971; Sugihara 2018; Taylor 1974; Ter Riet 1995; Theilla 2007; Van Anholt 2010; Wong 2014; Yamanaka 2017). Authors from two studies mentioned that they received no funding for their study (Leigh 2012; Theilla 2012). In nine studies, the research was financed by non-commercial sponsorships like government funding, research grants or financing by medical centres (Anbar 2014; Banks 2016; Botella Carretero 2008; Bourdel Marchasson 2000; Dennis 2005; Desneves 2005; Ek 1991; Ohura 2011; Pouyssegur 2015). Seven studies provided no information on funding or sponsorship (Arias 2008; Benati 2001; Brewer 1967; Chernoff 1990; Derossi 2009; Miu 2021; Yu 2015).

Excluded studies

We excluded 56 studies from the review based on full-text assessment. Of these, 24 studies turned out to not be RCTs and one to have been terminated. A further 15 studies did not measure pressure ulcers as an outcome (ACTRN12610000526077; Actrn 2021; Doig 2013; Langkamp-Henken 2000; Mehl 2021; NCT00507650; NCT03627910; NCT00135590; NCT00163007; NCT02711839; NCT03658278; Olvera 2014; Pineda Juarez 2016; Singer 2019; JPRN-UMIN000002072), five studies mentioned pressure ulcers as possible side effects but did not report them or it was unclear if these were new-onset pressure ulcers (Delmi 1990; Harvey 2016; Lauque 2004; Starke 2011; Vahabzadeh 2019), 10 studies did not assess a nutritional intervention or not as the sole intervention (Candela-Zamora 2010; IRCT20160914029817N8 2018; IRCT20190824044595N 2020; Landes 2016; Lu 2019; Lupianez Perez 2013; Lupianez Perez 2017; Olofsson 2007; Settel 1969; Zhang 2021), and one study assessed patients with chronic wounds instead of patients with pressure ulcers (Bauer 2013). Detailed reasons for excluding these 57 studies are described in Characteristics of excluded studies.

Ongoing studies and studies awaiting classification

We identified eight ongoing studies, seven in clinical trials registers and one protocol in a database (see Ongoing studies). Where the progress of the study was not clear or the study seemed to be finished, we contacted the principal investigators, but either they did not respond or confirmed that the study was not yet completed. We classified six reports as awaiting assessment (Studies awaiting classification). All of the records for these studies were conference abstracts, with too little information on methods and results to include them. A closer look at the study characteristics of the records by Ogawa 2021 showed that three of them reported on the same investigation. We contacted the authors of the conference abstracts, but without success in two cases. The main author of the study, Loreto Alvarez-Nebreda 2021 informed us that the paper was currently being submitted but not yet accepted or published.

Risk of bias in included studies

All included studies were prospective RCTs. In general, most of the studies included in the review were small and had either an overall risk of bias of either 'some concerns' or 'high risk'. We rated half of the studies with a high overall risk of bias in each of the primary outcomes. Five of these were prevention studies that addressed the incidence of new pressure ulcers, 12 studies focused on treatment for pressure ulcer healing. We rated only one study as low risk of bias when assessing completely healed ulcers and ulcer sizes. Figure 1, Figure 2 and Figure 3 show judgements about the risk of bias of all the included studies. We found no differences in the risk of bias with regard to two outcomes (incidence of new pressure ulcers and pressure ulcer healing). The descriptions of the respective risk of bias of each item can be found in the risk of bias tables; and for each included study, they are noted in the respective study description (Included studies). In addition, a detailed risk of bias assessment (RoB 2) of each study is available online. In this section, we provide summaries of the risk of bias assessments for each primary outcome.

Prevention studies

Energy, protein and micronutrients versus standard diet

Incidence of pressure ulcers

Three studies (high overall risk of bias) examined the effect of energy, protein and micronutrients on pressure ulcer incidence (Arias 2008; Bourdel Marchasson 2000; Ek 1991). One study was at high risk of bias arising from the randomization process; in the other two studies our risk of bias judgement was some concerns. We assessed risk of bias due to deviations from intended interventions as high in two studies and as some concerns in one study. Risk of bias due to missing outcome data was high in two studies and low in one study. Risk of bias in measurement of the outcome was high in one study and some concerns in two studies. For all included studies, we assessed the risk of bias in selection of the reported result as some concerns.

Protein, arginine, zinc and antioxidants versus placebo

Incidence of pressure ulcers

One study (overall risk of bias some concerns) examined the effect of protein, arginine, zinc and antioxidants on pressure ulcer incidence (Houwing 2003). We assessed risk of bias due to the randomization process and risk of bias in selection of reported results as some concerns, while we assessed risk of bias bias due to deviations from intended interventions, risk of bias due to missing outcome data and risk of bias in measurement of the outcome as low.

L-carnitine, L-leucine, calcium, magnesium and vitamin D versus standard diet

Incidence of pressure ulcers

One study (high overall risk of bias) examined the effect of L-carnitine, L-leucine, calcium, magnesium and vitamin D on pressure ulcer incidence (Derossi 2009). We assessed risks of bias arising from the randomization process, due to missing outcome data, in measurement of the outcome and in selection of reported results as some concerns, while we assessed risk of bias due to deviations from intended interventions as high.

EPA, GLA and antioxidants versus standard diet

Incidence of pressure ulcers

One study (overall risk of bias some concerns) examined the effect of EPA, GLA and antioxidants on pressure ulcer incidence (Theilla

2007). We assessed risk of bias due to randomization process and risk of bias in selection of reported results as some concerns, while we assessed risks of bias due to deviations from intended interventions, due to missing outcome data and in measurement of the outcome as low.

Protein versus standard diet

Incidence of pressure ulcers

Four studies examined the effect of protein on pressure ulcer incidence (Anbar 2014; Botella Carretero 2008; Dennis 2005; Hartgrink 1998). Except for one study with a high overall risk of bias (Dennis 2005), our overall risk of bias for the remaining three studies was some concerns (Anbar 2014; Botella Carretero 2008; Hartgrink 1998). Our judgement in one study for risk of bias arising from the randomization process was some concerns, while we rated this risk as low in the three other studies. We assessed the risk of bias due to deviations from intended interventions as some concerns in two studies and as low in the other two studies. Risk of bias due to missing outcome data was some concerns in one study and low in three studies. The risk of bias in measurement of the outcome was high in one study and some concerns in three studies. Risk of bias in selection of the reported result was low in one study and some concerns in three studies.

Disease-specific versus standard diet

Incidence of pressure ulcers

One study (overall risk of bias some concerns) examined the effect of a disease-specific diet on pressure ulcer incidence (Craig 1998). We assessed risks of bias due to randomization process, due to deviations from intended interventions, due to missing outcome data, in measurement of the outcome and in selection of reported results as some concerns.

Treatment studies

Energy, protein and micronutrients versus standard diet

Pressure ulcers healed

Three studies (high overall risk of bias) examined the effect of energy, protein and micronutrients on pressure ulcer healing (Ek 1991; Ohura 2011; Yu 2015). Our judgement for risk of bias arising from the randomization process in one study was some concerns, while this risk was high in two studies. We assessed the risk of bias due to deviations from intended interventions as high in two studies and as some concerns in one study. Risk of bias due to missing outcome data was high in two studies and low in one study. We assessed the risk of bias in measurement of the outcome and in selection of the reported result as some concerns for all included studies.

Protein, arginine, zinc and antioxidants versus standard diet or placebo

Pressure ulcers healed

Two studies (overall risk of bias high or some concerns) examined the effect of protein, arginine, zinc and antioxidants on pressure ulcer healing (Cereda 2009; Van Anholt 2010). Our judgement for one study for risk of bias arising from the randomization process was some concerns, while this risk was high in the other study. We assessed the risk of bias due to deviations from intended interventions and the risk of bias in measurement of the outcome as low in both studies. Risk of bias due to missing outcome data and in selection of the reported result were low in one study and some concerns in the other study.

Change in pressure ulcer area or depth or volume

Two studies (overall risk of bias high or some concerns) examined the effect of protein, arginine, zinc and antioxidants on the change in pressure ulcer area (cm^2; Cereda 2009; Van Anholt 2010). Our judgement for one study for risk of bias arising from the randomisation process was some concerns, while this risk was high in the other study. We assessed the risk of bias due to deviations from intended interventions and the risk of bias in measurement of the outcome as low in both studies. Risks of bias due to missing outcome data and in selection of the reported result were low in one study and some concerns in the other study.

Progress of healing

Three studies examined the effect of protein, arginine, zinc and antioxidants on the progress of healing, assessed with PUSH score (Cereda 2009; Desneves 2005; Van Anholt 2010). Two studies were at high overall risk of bias, and overall risk of bias for the remaining study was some concerns. Our judgement for one study for risk of bias arising from the randomization process was some concerns; in the other two studies, we assessed this risk as high. We assessed the risk of bias due to deviations from intended interventions and the risk of bias in measurement of the outcome as low in all three studies. Risk of bias due to missing outcome data was low in two studies and some concerns in one study. Risk of bias in selection of the reported result was low in one study and some concerns in two studies.

Arginine and micronutrients versus standard diet or placebo

Pressure ulcers healed

One study (low overall risk of bias) examined the effect of arginine and micronutrients on pressure ulcer healing (Cereda 2015). We assessed risks of bias arising from the randomization process, due to deviations from intended interventions, due to missing outcome data, in measurement of the outcome and in selection of the reported result as low.

Change in pressure ulcer area or depth or volume

One study (high overall risk of bias) examined the effect of arginine and micronutrients on the change in pressure ulcer area (cm^2; Banks 2016). Our judgements for risks of bias arising from the randomization process, due to deviations from intended interventions and in measurement of the outcome were some concerns, while risk of bias due to missing outcome data was high and risk of bias in selection of the reported result was low.

Two studies examined the effect of arginine and micronutrients on the percentage change in pressure ulcer area (Banks 2016; Cereda 2015). One study was at low overall risk of bias and the other at high overall risk of bias. Risk of bias arising from the randomization process, risk of bias due to deviations from intended interventions and risk of bias in measurement of the outcome were some concerns in one study and low in the other study. Risk of bias due to missing outcome data was high in one study and low in the other study, and we assessed risk of bias in selection of the reported result as low in both studies.

Progress of healing

One study (high overall risk of bias) examined the effect of arginine and micronutrients on the progress of healing, assessed with the PUSH score (Banks 2016). Risks of bias arising from the randomization process, due to deviations from intended interventions and in measurement of the outcome were some concerns, while risk of bias due to missing outcome data was high and we assessed risk of bias in selection of the reported result as low.

One study (overall risk of bias some concerns) examined the effect of arginine and micronutrients on the progress of healing, assessed with the DESIGN-R score (Yamanaka 2017). We assessed risk of bias arising from the randomization process, risk of bias due to deviations from intended interventions, risk of bias due to missing outcome data and risk of bias in measurement of the outcome as low. We assessed risk of bias in selection of the reported result as some concerns.

Different doses of arginine

Progress of healing

One study (high overall risk of bias) examined the effect of different doses of arginine on the progress of healing, assessed with the PUSH score (Leigh 2012). We assessed risks of bias arising from the randomization process and in measurement of the outcome as low, while risk of bias due to deviations from intended interventions was high and risks of bias due to missing outcome data and in selection of the reported result were some concerns.

EPA, GLA and antioxidants versus standard diet

Pressure ulcers healed

One study (overall risk of bias some concerns) examined the effect of EPA, GLA and antioxidants on pressure ulcer healing (Theilla 2007). We assessed risk of bias arising from the randomization process and risk of bias in selection of the reported result as some concerns, while risks of bias due to deviations from intended interventions, due to missing outcome data and in measurement of the outcome were low.

Progress of healing

One study (overall risk of bias some concerns) examined the effect of EPA, GLA and antioxidants on the progress of healing, assessed with the PUSH score (Theilla 2012). Risk of bias arising from the randomization process, risk of bias due to deviations from intended interventions and risk of bias in measurement of the outcome were some concerns, while we assessed risks of bias due to missing outcome data and in selection of the reported result as low.

Protein versus standard diet

Pressure ulcers healed

One study (overall risk of bias some concerns) examined the effect of protein on pressure ulcer healing (Chernoff 1990). We assessed risks of bias arising from the randomization process, due to deviations from intended interventions, in measurement of the outcome and in selection of the reported result as some concerns, while risk of bias due to missing outcome data was low.

One study (high overall risk of bias) examined the effect of protein on pressure ulcer episodes (Pouyssegur 2015). We assessed risks of bias arising from the randomization process, due to deviations from intended interventions, due to missing outcome data and in measurement of the outcome as high, and risk of bias in selection of the reported result as some concerns.

Progress of healing

One study (high overall risk of bias) examined the effect of protein on the progress of healing, assessed with the PUSH score (Desneves 2005). We assessed risk of bias arising from the randomization process as high; risks of bias due to deviations from intended interventions, due to missing outcome data and in measurement of the outcome were low, while risk of bias in selection of the reported result was some concerns.

Collagen versus standard diet or placebo

Change in pressure ulcer area or depth or volume

One study (overall risk of bias some concerns) examined the effect of collagen on the change in pressure ulcer area (cm^2; Sugihara 2018). We assessed risk of bias arising from the randomization process as unclear, while risks of bias due to deviations from intended interventions, due to missing outcome data, in measurement of the outcome and in selection of the reported result were low.

Progress of healing

Two studies examined the effect of collagen on the progress of healing, assessed with the PUSH score (Lee 2006; Sugihara 2018). Overall risk of bias was high in one study and some concerns in the other study. We assessed risk of bias arising from the randomization process as high in one study and some concerns in the other study, while risks of bias due to deviations from intended interventions, due to missing outcome data and in selection of the reported result were some concerns in one study and low in the other study; risk of bias in measurement of the outcome was low in both studies.

One study (overall risk of bias some concerns) examined the effect of collagen on the progress of healing, assessed with the DESIGN-R score (Yamanaka 2017). We assessed risks of bias arising from the randomization process, due to deviations from intended interventions, due to missing outcome data and in measurement of the outcome as low, while risk of bias in selection of the reported result was some concerns.

Specialized amino acid mixture (arginine-enriched) versus standard diet or placebo

Progress of healing

One study (overall risk of bias some concerns) examined the effect of a specialized arginine-enriched amino acid mixture on the progress of healing, assessed with the PUSH score (Wong 2014). We assessed risk of bias arising from the randomization process, risk of bias in measurement of the outcome, risk of bias due to missing outcome data and risk of bias in selection of the reported result as low, while risk of bias due to deviations from intended interventions was some concerns.

Ornithine alpha-ketoglutarate versus placebo

Change in pressure ulcer area or depth or volume

One study (overall risk of bias some concerns) examined the effect of ornithine alpha-ketoglutarate on the change in pressure ulcer

area (cm^2 and percentage; Meaume 2009). We assessed risks of bias arising from the randomization process, due to deviations from intended interventions and due to missing outcome data as low, while risk of bias in measurement of the outcome and risk of bias in selection of the reported result were some concerns.

Vitamin C versus placebo

Pressure ulcers healed

Two studies examined the effect of vitamin C on pressure ulcer healing (Taylor 1974; Ter Riet 1995). One study was at high overall risk of bias and the other was some concerns. We assessed risk of bias arising from the randomization process, as some concerns In one study, and high in the other study. We assessed the risk of bias due to deviations from intended interventions as some concerns in one study and as low in the other study. Risk of bias due to missing outcome data and risk of bias in measurement of the outcome were low in both studies, and risk of bias in selection of the reported result was some concerns in both studies.

Change in pressure ulcer area or depth or volume

One study (high overall risk of bias) examined the effect of vitamin C on the change in pressure ulcer area (percentage; Taylor 1974). We assessed risk of bias arising from the randomization process as high, and risks of bias due to deviations from intended interventions and in selection of the reported result as some concerns, while risk of bias due to missing outcome data and risk of bias in measurement of the outcome were low.

Zinc sulphate versus placebo

Pressure ulcers healed

One study (overall risk of bias some concerns) examined the effect of zinc sulphate on pressure ulcer healing (Brewer 1967). We assessed risk of bias arising from the randomization process, risk of bias due to deviations from intended interventions and risk of bias in measurement of the outcome as low, while risks of bias due to missing outcome data and in selection of the reported result were some concerns.

Change in pressure ulcer area or depth or volume

One study (high overall risk of bias) examined the effect of zinc sulphate on the change in pressure ulcer volume (mL; Norris 1971). We assessed the risks of bias arising from the randomization process, due to deviations from intended interventions and in selection of the reported result as some concerns, while risk of bias due to missing outcome data was high and risk of bias in measurement of the outcome was low.

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Energy, protein and micronutrients compared to standard diet for the prevention of pressure ulcers; **Summary of findings 2** Summary of findings table - Protein compared to standard diet for the prevention of pressure ulcers; **Summary of findings 3** Summary of findings table - Energy, protein and micronutrients compared to standard diet for treating pressure ulcers; **Summary of findings 4** Summary of findings table - Protein, arginine, zinc and antioxidants compared to standard diet or placebo for treating pressure ulcers; **Summary of findings 5** Summary of findings table - Arginine and micronutrients compared to standard diet for treating pressure ulcers; **Summary of findings 6** Summary of findings table - Collagen compared to standard diet or placebo for treating pressure ulcers

The included studies were heterogeneous with regard to participants and to nutritional interventions. Only a few studies examined comparable nutritional supplements, which is why we did not conduct subgroup analyses (setting-specific, patient characteristics-specific). In addition, all studies administered the supplements enterally.

We did not perform any prespecified sensitivity analyses because most included studies had an overall risk of bias of 'some concerns' or 'high', and none of the meta-analyses included studies with low and high overall risk of bias. An overview of types of nutritional interventions is presented in Figure 5.

Evidence from prevention studies

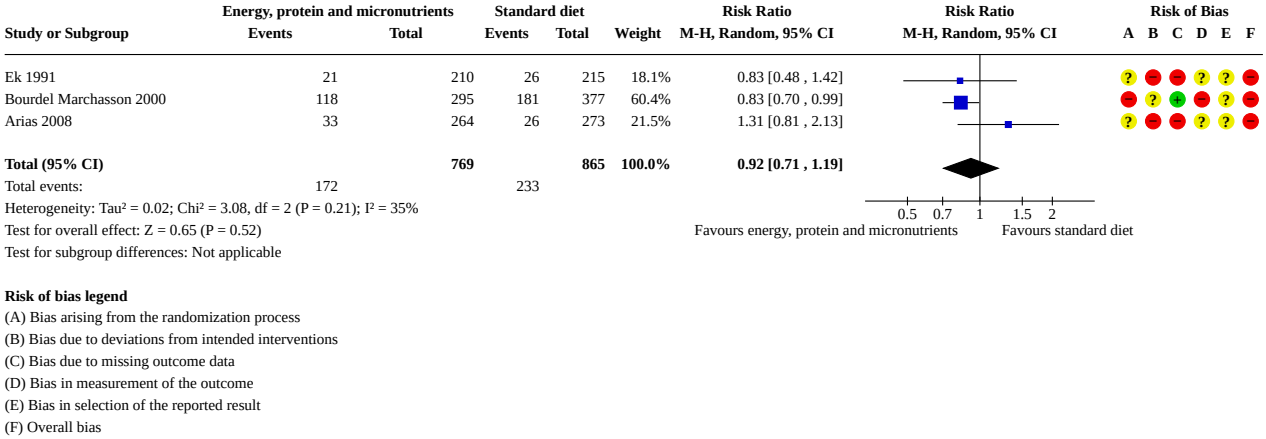
Eleven included studies were related to pressure ulcer prevention. The primary outcome in prevention studies was the proportion of participants who developed new pressure ulcers.

Energy, protein and micronutrients compared with standard diet (3 studies)

Pressure ulcer incidence

When we pooled 1634 participants from the three studies on energy, protein and micronutrients supplements (Arias 2008; Bourdel Marchasson 2000; Ek 1991), using a random-effects model, we found there may be little to no difference in the incidence of pressure ulcers between the intervention and control groups (RR 0.92, 95% CI 0.71 to 1.19; P = 0.52, I^2 = 35%; low-certainty evidence; Analysis 1.1; Figure 6; Summary of findings 1). We downgraded the evidence by two levels to low certainty due to very serious risk of bias (we rated all included studies as high overall risk of bias).

Figure 6. Comparison 1. Energy, protein and micronutrients versus standard diets for pressure ulcer prevention, outcome 1: incidence of pressure ulcers



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

None of the remaining prespecified review outcomes were reported.

Protein, arginine, zinc and antioxidants compared with placebo (1 study)

Pressure ulcer incidence

Houwing 2003 included 103 hip fracture patients who were followed up for 28 days. There may be little to no difference between the two groups, but the evidence is very uncertain. The incidence of pressure ulcers (stages 1 to 2) in the nutritional intervention group was 27/51 (55%) compared with 30/52 (59%) in the placebo group (RR 0.92, 95% CI 0.65 to 1.30; very low-certainty evidence; Analysis 2.1; Appendix 9).We downgraded the evidence by one level due to serious risk of bias (we rated risk of bias as some concerns) and by two levels for very serious imprecision (wide 95% CI overlaps the line of null effect and includes potential benefit and harm as well as a low number of participants and events).

None of the participants developed a pressure ulcer surpassing stage 2, but the incidence of stage 2 pressure ulcers was 18% in the nutritional intervention group versus 28% in the placebo group (RR 0.66, 95% CI 0.31 to 1.38).

None of the remaining prespecified review outcomes were reported.

L-carnitine, L-leucine, calcium, magnesium and vitamin D compared with standard diet (1 study)

Pressure ulcer incidence

Derossi 2009 included 107 hip-fracture patients aged 65 and older, scheduled to undergo surgical treatment. There may be little to no difference in pressure ulcer incidence at the end of the 40-day study between the two groups, but the evidence is very uncertain (nutritional intervention group 3/38 (7.89%) compared with the control group 6/41 (14.63%); RR 0.54, 95% CI 0.15 to 2.01; very low-certainty evidence; Analysis 3.1; Appendix 10). We downgraded the evidence by one level due to serious risk of bias (we rated risk of bias as some concerns) and by two levels for very serious imprecision (95% CI overlaps the line of null effect and includes potential benefit and harm as well as a low number of participants and events).

None of the remaining prespecified review outcomes were reported.

EPA, GLA and antioxidants compared with standard diets (1 study)

Pressure ulcer incidence

Theilla 2007 included 100 intensive care patients suffering from acute lung injury and compared a high fat and low carbohydrate enteral formula, which was enriched in EPA, GLA, and vitamins A, C, and E. There may be little to no difference between the two groups in pressure ulcer development, but the evidence is very uncertain. There were three new pressure ulcers in the supplemented group compared with one in the control group on day seven (RR 3.20, 95% CI 0.34 to 29.63; very low-certainty evidence; Analysis 4.1; Appendix 11). We downgraded the evidence by one level due to serious risk of bias (we rated risk of bias as some concerns) and by two levels for very serious imprecision (95% CI overlaps the line of null effect and includes potential benefit and harm and a low number of participants and events).

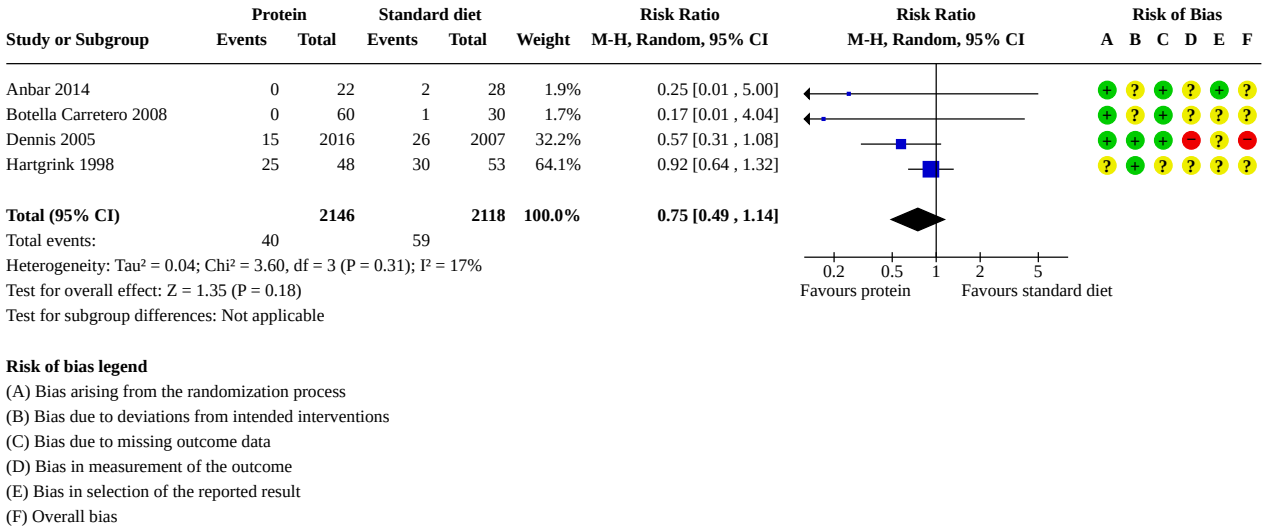
None of the remaining prespecified review outcomes were reported.

Protein supplements compared with standard diet (4 studies)

Pressure ulcer incidence

Hartgrink 1998, Dennis 2005, Botella Carretero 2008 and Anbar 2014 included 4264 participants in the four studies investigating protein-enriched supplements. Pooled data, using a random-effects model, suggests that protein-enriched supplements may result in little to no difference in reducing pressure ulcer incidence (RR 0.75, 95% CI 0.49 to 1.14; P = 0.18, I^2 = 17%; low-certainty evidence; Analysis 5.1; Figure 7; Summary of findings 2). We downgraded the evidence by one level due to serious risk of bias (we rated three out of four studies as some concerns) and by one level for imprecision (95% CI overlaps the line of null effect and includes potential benefit and harm and a low number of events).

Figure 7. Comparison 5. Protein supplements versus standard diets for pressure ulcer prevention, outcome 1: incidence of pressure ulcers

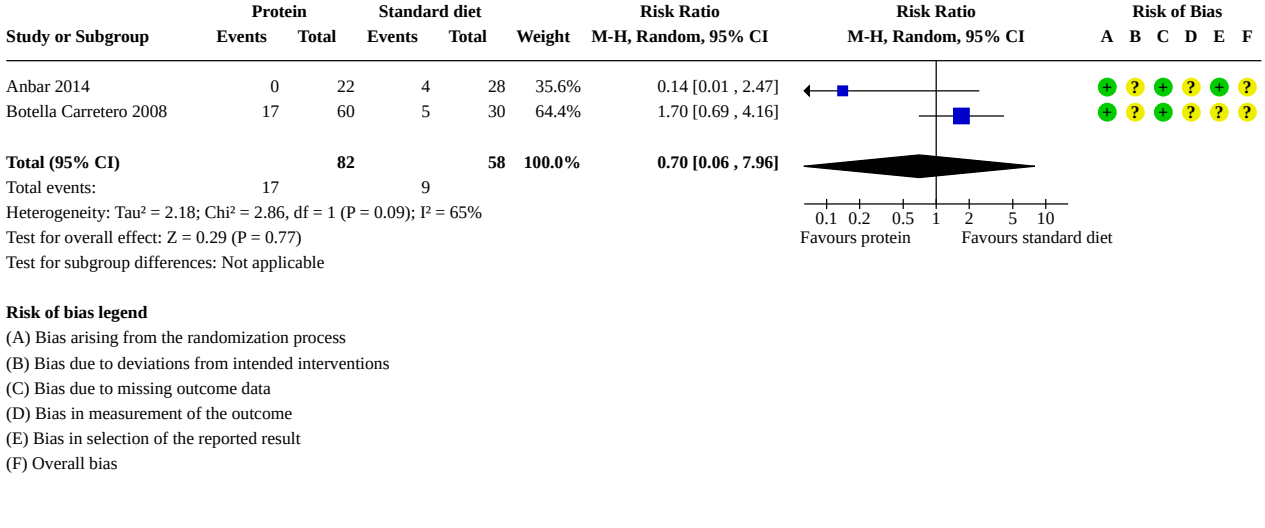


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Side effects

Regarding gastrointestinal side effects, we pooled data from two studies (Botella Carretero 2008; Anbar 2014), using a random-effects model. There may be little to no difference between the two groups, but the evidence is very uncertain (RR 0.70, 95% CI 0.06 to 7.96; P = 0.77, I^2 = 65%; very low-certainty evidence; Analysis 5.2; Figure 8; Summary of findings 2). We downgraded the evidence by one level due to serious risk of bias (we rated both studies as some concerns) and by two levels for very serious imprecision (95% CI overlaps the line of null effect and includes potential benefit and harm as well as a low number of participants and events).

Figure 8. Comparison 5. Protein supplements versus standard diets for pressure ulcer prevention, outcome 2: gastrointestinal side effects



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

None of the remaining prespecified review outcomes were reported.

Disease-specific diet compared with a standard diet (1 study)

Pressure ulcer incidence

Craig 1998 included 34 people with a history of type 2 diabetes mellitus or documented hyperglycaemia who required total enteral nutrition support by nasogastric tube. A disease-specific, reduced-carbohydrate, modified-fat formula was compared with a standard high-carbohydrate formula. Information on pressure ulcer incidence was available from 27 (79.41%) people. There may be little to no difference in pressure ulcer incidence between the two groups, but the evidence is very uncertain (6/14 (42.86%) developed a pressure ulcer in the treatment group compared with 7/13 (53.85%) in the control group; RR 0.80, 95% CI 0.36 to 1.75; P = 0.57; very low-certainty evidence; Analysis 6.1; Appendix 12). We downgraded the evidence by one level due to serious risk of bias (we rated risk of bias as some concerns) and by two levels due to very serious imprecision (95% CI overlaps the line of null effect

and includes potential benefit and harm as well as a low number of participants and events).

None of the remaining prespecified review outcomes were reported.

Evidence from treatment studies

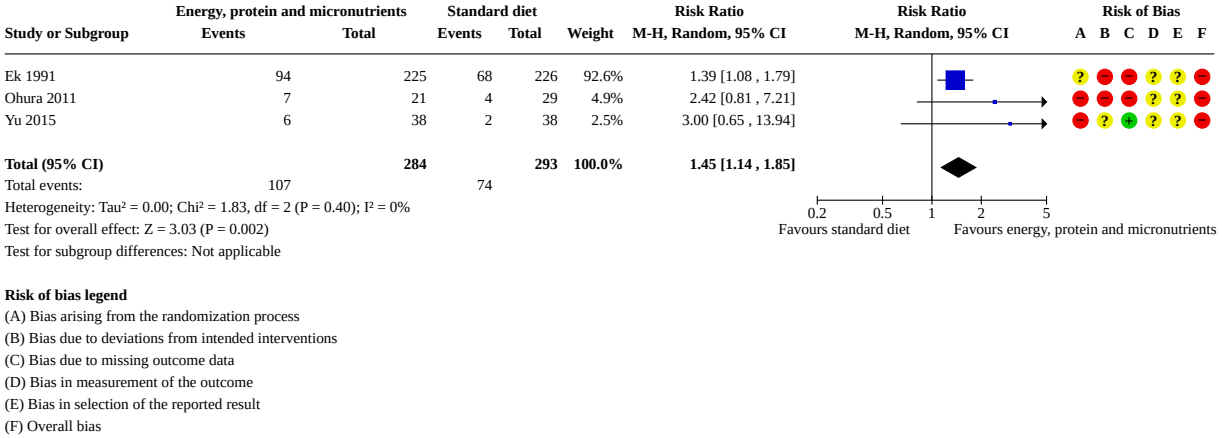
A total of 24 studies were related to pressure ulcer treatment. Both Benati 2001 and Desneves 2005 were three-arm studies that compared a protein, arginine, zinc, and antioxidant-supplemented group with a protein-supplemented group and a standard-diet group, respectively. Yamanaka 2017 was another three-arm study that compared the treatment effect of arginine and micronutrients as a treatment arm and collagen as another treatment arm with a standard diet. Sugihara 2018 was another three-arm study that compared different collagen supplements (collagen with low dipeptide and collagen with high dipeptide) with placebo.

Energy, protein and micronutrient compared with standard diet (3 studies)

Number of people healed

Three studies, including 577 participants, reported the number of people who had a completely healed pressure ulcer. We combined data from Ek 1991, Ohura 2011 and Yu 2015 using a random-effects model. The energy, protein and micronutrient supplements may result in more people with a completely healed pressure ulcer compared with those on a standard diet (RR 1.45, 95% CI 1.14 to 1.85, P = 0.002, I^2 = 0%; low-certainty evidence; Analysis 7.1; Figure 9; Summary of findings 3). We downgraded the certainty of evidence by two levels for very serious risk of bias (we rated all studies as high risk of overall bias).

Figure 9. Comparison 7. Energy, protein and micronutrients versus standard diets for pressure ulcer treatment, outcome 1: number of people healed



Side effects

Ohura 2011 presented data on study-related adverse events reported by tube-fed patients and found that there may be little to no difference in self-reported side effects between the two groups, but the evidence is very uncertain (8/30 (26.67%) in the treatment group and 5/30 (16.67%) in the control group; RR 1.60, 95% CI 0.59 to 4.33; P = 0.36; very low-certainty evidence; Analysis 7.2; Summary of findings 3). We downgraded the certainty of evidence by one level for serious risk of bias (we rated the study as high risk of overall bias) and by two levels for very serious imprecision (95% CI overlaps the line of null effect and includes potential benefit and harm and a low number of participants and events). No further details on the types of side effects were presented.

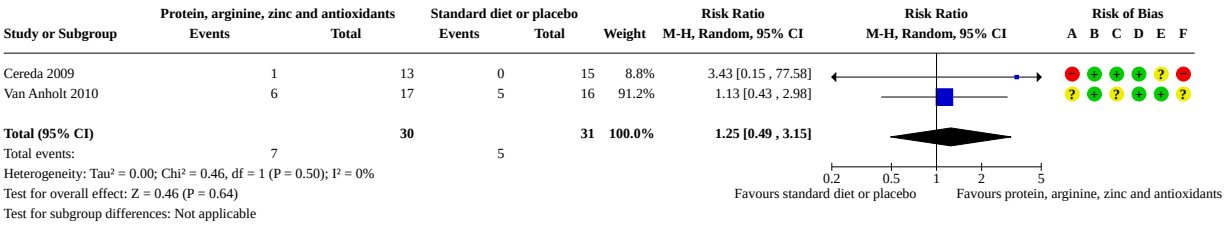
None of the remaining prespecified review outcomes were reported.

Protein, arginine, zinc and antioxidants compared with standard diet or placebo (4 studies)

Number of people healed

Cereda 2009 and Van Anholt 2010 provided data on 61 participants. There may be little to no difference between the nutrition intervention and the control group with respect to the number of people with healed pressure ulcers, but the evidence is very uncertain (RR 1.25, 95% CI 0.49 to 3.15; P = 0.64, I^2 = 0%; very low-certainty evidence; Analysis 8.1; Figure 10; Summary of findings 4). We downgraded the evidence by one level for serious risk of bias (we rated risk of bias with more weight as some concerns about risk of bias) and by two levels for very serious imprecision (low number of participants and events).

Figure 10. Comparison 8. Protein, arginine, zinc and antioxidants versus standard diets or placebo for pressure ulcer treatment, outcome 1: number of people healed

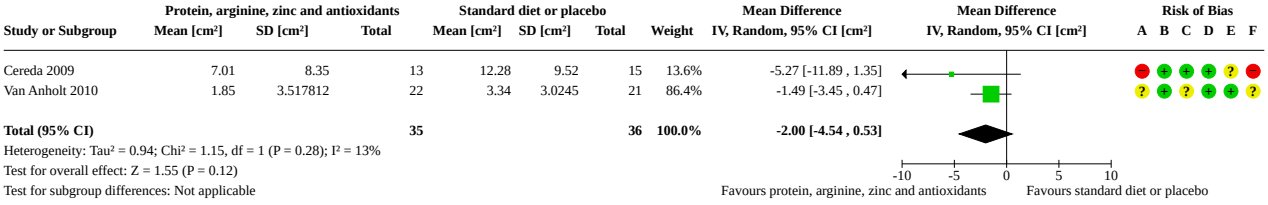


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Ulcer size

We were able to pool data from Cereda 2009 and Van Anholt 2010, which both assessed differences in mean pressure ulcer size (I^2 = 13%). Overall, the evidence is very uncertain about the treatment effect of the protein, arginine, zinc and antioxidants supplement compared with a standard diet or placebo (MD −2.00, 95% CI −4.54 to 0.53; very low-certainty evidence; Analysis 8.2; Figure 11; Summary of findings 4). We downgraded the certainty of evidence by one level for serious risk of bias (we rated the risk of bias of the study with more weight as some concerns) and by two levels for very serious imprecision (wide 95% CI and a low number of participants).

Figure 11. Comparison 8. Protein, arginine, zinc and antioxidants versus standard diets or placebo for pressure ulcer treatment, outcome 1: ulcer size (change in pressure ulcer area in cm^2)



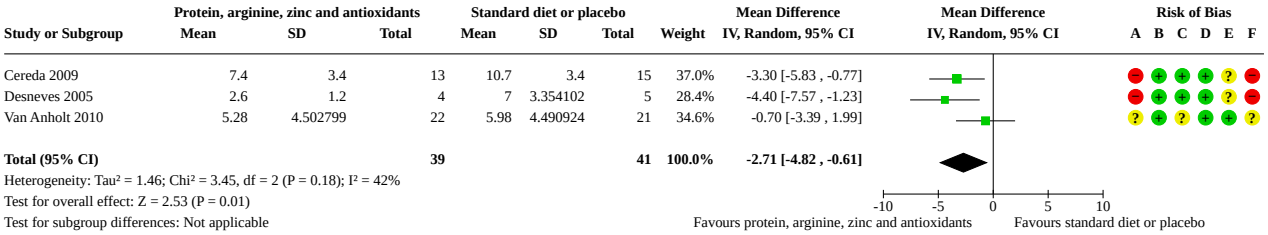
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Rate of ulcer healing

Benati 2001 undertook a preliminary investigation but presented the results on the PSST scores in graphical form only, with no numerical data. The quality of the graph was poor, and it was impossible to extrapolate data. The participants who received protein, arginine, zinc and antioxidant supplements (intervention group 1) or protein supplements (intervention group 2) had a more rapid improvement in pressure ulcer healing over the 15-day intervention period compared with those who received a standard diet.

Three other studies used the PUSH scoreas an outcome, and therefore we combined PUSH data fromDesneves 2005, Van Anholt 2010 and Cereda 2009 using a random-effects model. Eighty participants were included and there may be improvement in PUSH scores in people who received the protein, arginine, zinc and antioxidants supplement compared with those on a standard diet or placebo, but the evidence is very uncertain (MD −2.71, 95% CI −4.82 to −0.61, P = 0.01, I^2 = 42%; very low-certainty evidence; Analysis 8.3; Figure 12).

Figure 12. Comparison 8. Protein, arginine, zinc and antioxidants versus standard diets or placebo for pressure ulcer treatment, outcome 3: rate of ulcer healing (PUSH score)



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Side effects

Van Anholt 2010 reported data on side effects (which were diarrhoea, nausea, vomiting, constipation, and dyspepsia) experienced during the study period among people aged between 18 and 90 years old recruited from healthcare centres, hospitals and long-term care facilities in four countries. Participants had at least one NPUAP stage 3 or 4 pressure ulcer. There may be little to no difference in the number of people who experience at least one side effect between the two groups but the evidence is very uncertain (16/22 (72.73%) in the treatment group compared with 13/21 (61.90%) in the control group; RR 1.17, 95% CI 0.77 to 1.79; P = 0.45; very low-certainty evidence; Analysis 8.4; Summary of findings 4). We downgraded the certainty of evidence by one level for serious risk of bias (we rated risk of bias as some concerns) and by two levels for very serious imprecision (95% CI overlaps the line of null effect and includes potential benefit and harm and a low number of participants and events). Nevertheless, the study authors reported that there were no differences in individual gastrointestinal side effects except constipation (4/22 (18.18%) in the treatment group compared with 0/21 (0%) in the control group had constipation in week 4; P = 0.029, Fisher's exact test).

None of the remaining prespecified review outcomes were reported.

Arginine and micronutrients compared with standard diet or placebo (3 studies)

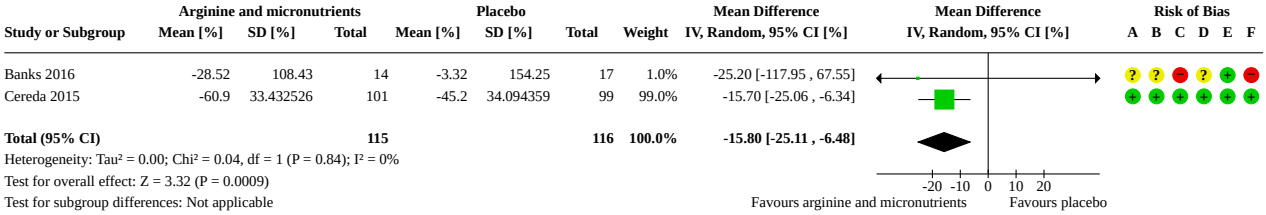
Number of people healed

Cereda 2015 included 200 malnourished long-term care residents or people receiving home-care services in seven sites, with NPUAP stage 2 to 4 pressure ulcers, who received either an arginine and micronutrient supplement or a placebo. There may be little to no difference between the two groups in the number of people whose ulcers healed (treatment group 17/101 (16.83%) and control group 10/99 (10.10%); RR 1.67, 95% CI 0.80 to 3.46; P = 0.17; low-certainty evidence; Analysis 9.1; Summary of findings 5). We downgraded the evidence by two levels due to very serious imprecision (small number of events and wide 95% CI which overlaps the no-effect line).

Ulcer size

Banks 2016 assessed the change in pressure ulcer area (in cm^2) and found that there may be little to no difference in pressure ulcer area between the group receiving arginine and micronutrient supplements compared to the group with a standard diet (MD −3.25, 95% CI −7.19 to 0.69; P = 0.11; low-certainty evidence; Analysis 9.2; Summary of findings 5). We downgraded the evidence by one level for high risk of bias and by one level for imprecision. However, we found a slight percentage reduction in pressure ulcer area in the group with arginine and micronutrient supplementation (Banks 2016, Cereda 2015) when pooling data (MD −15.80, 95% CI −25.11 to −6.48; P = 0.0009, I^2 = 0%; low-certainty evidence; Analysis 9.3; Figure 13; Summary of findings 5). We downgraded the evidence by one level due to serious risk of bias (one of two studies had a high overall risk of bias) and by one level due to serious imprecision (low number of participants).

Figure 13. Comparison 9. Arginine and micronutrients versus standard diets or placebo for pressure ulcer treatment, outcome 3: ulcer size (percentage change in pressure ulcer area)



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Rate of ulcer healing

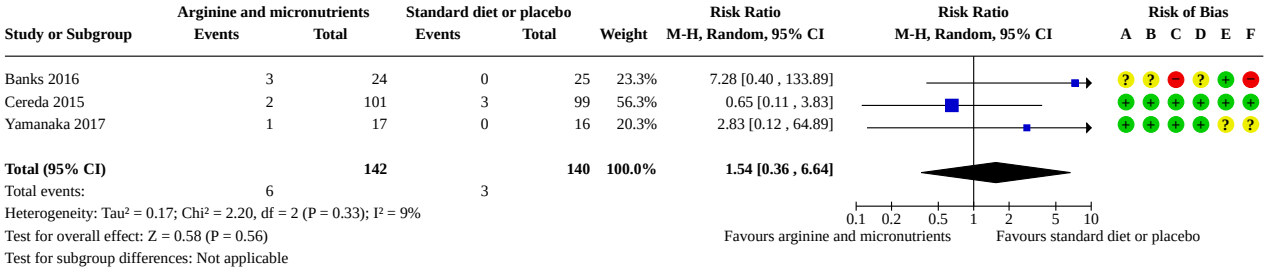
Banks 2016 examined the treatment effect of arginine and micronutrients supplements on the PUSH score and found that there may be little to no difference in treatment effect, but the evidence is very uncertain (MD −0.48, 95% CI −3.80 to 2.84; P = 0.78; very low-certainty evidence; Analysis 9.4).

Yamanaka 2017 was a three-arm study and included 51 orally or tube-fed patients who received either an arginine and micronutrient supplement, a collagen and micronutrient supplement, or a standard diet. When comparing the mean DESIGN-R scores in the arginine and micronutrient supplement group with the standard diet group, there may be little to no difference between the two groups, but the evidence is very uncertain (MD −1.60, 95% CI −9.53 to 6.33; P = 0.69; very low-certainty evidence; Analysis 9.5).

Side effects

Banks 2016, Cereda 2015 and Yamanaka 2017 reported data on gastrointestinal intolerance including nausea and diarrhoea. There may be little to no difference in side effects occurring during the study period between the arginine and micronutrients supplement group and the standard diet or placebo group after we pooled the data using a random-effects model, but the evidence is very uncertain (RR 1.54, 95% CI 0.36 to 6.64; P = 0.56, I^2 = 9%; very low-certainty evidence; Analysis 9.6; Figure 14; Summary of findings 5). We downgraded the evidence by one level due to serious risk of bias (we rated one study at high risk of bias) and twice for very serious imprecision (95% CI overlaps the line of null effect and includes potential benefit and harm and a low number of participants and events).

Figure 14. Comparison 9. Arginine and micronutrients versus standard diets or placebo for pressure ulcer treatment, outcome 6: side effects (at least one adverse gastrointestinal effect)



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Cost of care

Cereda 2015 compared the costs of the formula used in the supplemented group and the placebo group and found the arginine and micronutrients supplement probably more costly compared with the placebo formula (MD EUR 39.40, 95% CI 27.57 to 51.23; P < 0.00001; moderate-certainty evidence; Analysis 9.7; Summary of findings 5). We downgraded this evidence to moderate certainty by one level due to serious imprecision (the 95% CI did not overlap the line of null effect, but the number of participants was low).

Acceptability: non-adherence

Banks 2016 reported information on the number of participants who did not adhere to the supplementation. There may be little to no difference in non-adherence between the two groups, but the evidence is very uncertain (7/24 participants did not adhere to the supplementation in the intervention group, while all 25 participants adhered to the standard diet (RR 15.60, 95% CI 0.94 to 259.00; P = 0.06; very low-certainty evidence; Analysis 9.8; Summary of findings 5). We downgraded the evidence by one level due to serious risk of bias (we rated the study as high risk of bias) and by two levels for very serious imprecision (wide 95% CI and a low number of participants).

None of the remaining prespecified review outcomes were reported.

Different doses of arginine (1 study)

Rate of ulcer healing

Leigh 2012 examined the effects of arginine and micronutrients in two different doses of arginine in a study with 29 participants. They assessed changes in pressure ulcer with the PUSH score and found that there may be little to no differences between the different doses of arginine, but the evidence is very uncertain (MD −0.60, 95% CI −4.33 to 3.13; very low-certainty evidence Analysis 10.1).

Side effects

The types of side effects were not specified, but in one case they led to termination of study participation (RR 2.81, 95% CI 0.12 to 63.83; very low-certainty evidence; Analysis 10.2; Appendix 13). We downgraded the evidence by one level for serious risk of bias (we rated the study as high risk of bias) and by two levels for very serious imprecision (wide 95% CI and a low number of participants).

Acceptability: non-adherence

Leigh 2012 reported information on the number of participants who did not adhere to the prescribed diet or supplementation and found that there may be little to no difference between the two groups, but the evidence is very uncertain (RR 1.09, 95% CI 0.08 to 15.41; very low-certainty evidence; Analysis 10.3; Appendix 13). We downgraded the evidence by one level for serious risk of bias (we rated the study as high risk of bias) and by two levels for very serious imprecision (wide 95% CI and a low number of participants).

None of the remaining prespecified review outcomes were reported.

EPA, GLA and antioxidants compared to standard diet (1 study)

Number of people healed

Theilla 2007 recruited 100 patients from intensive care suffering from acute lung injury. The study compared a high-fat and low-carbohydrate enteral formula enriched in lipids with ß-carotene, vitamin C and E with a high-fat and low-carbohydrate enteral formula. The evidence is very uncertain about the enriched formula in relation to ulcer healing. Neither group had healed ulcers on day 7 of the study (very low-certainty evidence; Analysis 11.1; Appendix 14 . We downgraded the evidence by one level for serious risk of bias (baseline imbalance, no allocation concealment, open-label study) and by two levels for very serious imprecision (low number of participants and no events).

Rate of ulcer healing

Theilla 2012 included 40 patients with pressure ulcers of NPUAP stage 2 or higher admitted to the intensive care unit of a hospital. Participants were either provided with high-energy/high-protein n-3 fatty acid-rich micronutrient supplements or a standard hospital diet and follow-up for 28 days. This study found there may be little to no difference in PUSH scores at day 28 between the two groups, but the evidence is very uncertain (MD −1.35, 95% CI −5.78 to 3.08; very low-certainty evidence; Analysis 11.2).

None of the remaining prespecified review outcomes were reported.

Protein compared to standard diet (4 studies)

Pressure ulcer healed

Chernoff 1990 compared 12 tube-fed people with pressure ulcers who were put on either a very high-protein formula or a high-protein formula and found that there may be little to no difference between the two groups in the number of people with completely healed ulcers within eight weeks, but the evidence is very uncertain (4/6 (66.67%) in the very high-protein formula group had completely healed ulcers compared to none in the high-protein formula group (0/6; 0%) (RR 9.00, 95% CI 0.59 to 137.65; P = 0.11; very low-certainty evidence; Analysis 12.1; Appendix 15). We downgraded the evidence by one level because of serious risk of bias (we rated risk of bias as some concerns) and by two levels due to very serious imprecision (95% CI overlaps the no-effect line and includes potential benefit and harm and a low number of events and participants).

Pressure ulcer episodes

Pouyssegur 2015 included 175 people aged 70 years or older in nursing homes who were diagnosed as malnourished based on a weight loss survey, BMI and Mini-Nutritional Assessment (MNA) screening tool. The supplemented group was provided with a protein supplement in the form of cookies for a period of six weeks. Pressure ulcer data were presented as changes in pressure ulcer episodes, which included both people with pressure ulcers at baseline and people with new pressure ulcers during the study period. Pouyssegur 2015 found that there may be little to no difference between the protein supplement group and the standard diet group, but the evidence is very uncertain (RR 1.15; 95% CI 0.38 to 3.46; very low-certainty evidence; Analysis 12.2; Appendix 15). We downgraded the evidence by two levels for very serious risk of bias (we rated almost all risk of bias domains as high) and by one level for serious imprecision (wide 95% CI and a low number of participants).

Rate of ulcer healing

Desneves 2005 used the PUSH score to assess the rate of ulcer healing. They found that there may be little to no difference in PUSH scores between their protein supplement and their standard diet group but the evidence is very uncertain (MD −1.00, 95% CI −2.76 to 0.76; P = 0.27; very low-certainty evidence; Analysis 12.3).

For this comparison, Benati 2001 also provided only graphically presented changes in PSST scores. Participants who received protein supplements seemed to have a more rapid improvement in pressure ulcer healing over the 15-day intervention period compared with those who received a standard diet.

Side effects

Pouyssegur 2015 provided information on gastrointestinal side effects from 152 (86.86%) people. There may be little to no difference in diarrhoea episodes between the two groups, (1/80 (1.25%) in the supplemented group compared with 6/72 (8.33%) in the control group), but the evidence is very uncertain (RR 0.15, 95% CI 0.02 to 1.22; P = 0.08; very low-certainty evidence; Analysis 12.4; Appendix 15). We downgraded the evidence by one level due to serious risk of bias (we rated the study as high risk of bias) and by two levels for very serious imprecision (95% CI overlaps the no-effect line and includes potential benefit and harm as well as a low number of events and participants).

Cost of care

In the economic assessment (from the healthcare perspective) of the Pouyssegur 2015 study using medical costs related to nutritional supplements and the care of pressure ulcers, diarrhoea, falls, and infections, the supplemented group may have lower healthcare costs (in Euros) than the control group (MD EUR −191.00, 95% CI −240.63 to −141.37; P < 0.00001; low-certainty evidence; Analysis 12.5; Appendix 15). We downgraded the evidence by one level due to serious risk of bias (we rated the study as high risk of bias) and by one level for serious imprecision (95% CI does not overlap the null effect line, but the number of participants was low).

None of the remaining prespecified review outcomes were reported.

Collagen versus standard diet or placebo (3 studies)

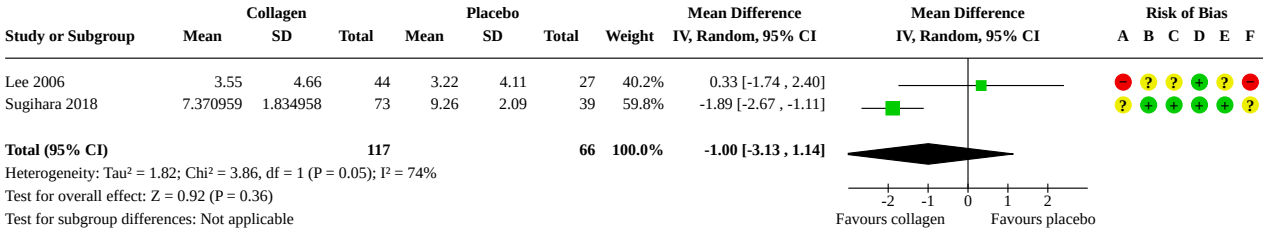
Ulcer size

Sugihara 2018 randomized 122 inpatients into three groups (collagen - low dipeptide, collagen - high dipeptide, and placebo). Ulcer size at 16 weeks was only reported in the high dipeptide collagen group and the placebo group. The study found that the collagen probably reduced ulcer sizes compared to the placebo group (MD −1.81 cm^2, 95% CI −3.36 to −0.26; moderate-certainty evidence; Analysis 13.1; Summary of findings 6). We downgraded the evidence by one level due to serious imprecision (although the 95% CI was narrow and did not overlap the null effect, the number of participants was low).

Rate of ulcer healing

Lee 2006 and Sugihara 2018 recruited 183 participants to examine the effects of collagen supplements compared with placebo on PUSH scores and found that there may be little to no difference in the rate of ulcer healing between these groups, but the evidence is very uncertain (MD −1.00, 95% CI −3.13 to 1.14; P = 0.36, I^2 = 74%; very low-certainty evidence; Analysis 13.2; Figure 15).

Figure 15. Comparison 13. Collagen versus standard diets or placebo for pressure ulcer treatment, outcome 2: rate of ulcer healing (PUSH score)



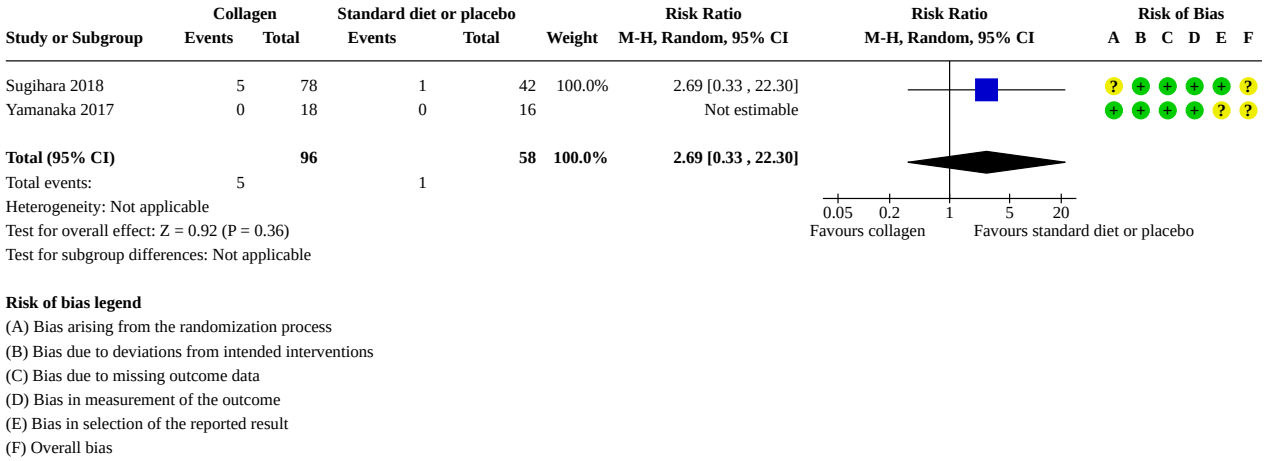
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Another three-arm study, Yamanaka 2017, used DESIGN-R scores to measure ulcer healing rates and found that collagen supplementation may reduce DESIGN-R scores at week 4 compared with the standard diet group, but the evidence is very uncertain (MD −6.00, 95% CI −10.76 to −1.24; P = 0.01; very low-certainty evidence; Analysis 13.3).

Side effects

Yamanaka 2017 assessed diarrhoea episodes during the study period and found none in the collagen supplement group or the standard diet group. In the two collagen-supplemented groups in Sugihara 2018, 2/39 (5.13%) participants in the low-dipeptide collagen group experienced moderate constipation and 1/39 (2.56%) participants experienced mild diarrhoea. In the high-dipeptide collagen group, 2/39 (5.13%) experienced moderate diarrhoea. In the placebo group, one participant experienced mild headache (1/42 (2.38%)). These reported side effects were resolved with concomitant medication and only persisted for one day. None of these side effects reappeared upon re-challenge. In summary, there may be little to no difference in side effects between the supplemented group and the placebo group but the evidence is very uncertain (RR 2.69, 95% CI 0.33 to 22.30; P = 0.36; very low-certainty evidence; Analysis 13.4; Figure 16; Summary of findings 6). We downgraded the evidence by one level because of serious risk of bias (we rated the risk of bias as some concerns) and by two levels due to very serious imprecision (95% CI overlaps the no-effect line and includes potential benefit and harm and a low number of events and participants).

Figure 16. Comparison 13: Collagen versus standard diets or placebo for pressure ulcer treatment, Outcome 4: Side effects (at least one adverse gastrointestinal effect)



None of the remaining prespecified review outcomes were reported.

Specialized amino acid mixture (arginine-enriched) compared with standard diet or placebo (2 studies)

Rate of ulcer healing

Wong 2014 included 23 hospital inpatients with grade 2 to 4 pressure ulcers and provided them with either the specialized amino acid (arginine-enriched) supplement in sachets or the placebo sachets with matched flavour for two weeks. There may be lower mean PUSH scores at week 2 in the supplemented group compared to the placebo group, but the evidence is very uncertain (MD −1.00, 95% CI −1.88 to −0.12; P = 0.03; very low-certainty evidence; Analysis 14.1). The study also reported data on the percentage decrease in ulcer area and healing rate per day and found a higher rate of ulcer healing in the placebo group (37.5% decrease in ulcer area in two weeks; 0.31 cm^2/day ulcer healing rate) compared with the supplemented group (27.5% decrease in ulcer area in two weeks; 0.24 cm^2/day ulcer healing rate).

Miu 2021 attempted to follow up Wong 2014 by providing the amino acid supplement for a longer period and with more participants. They included 87 hospital patients aged 18 or older with EPUAP stage 3 and 4 pressure ulcers and provided them with either amino acid supplements or a standard diet for four weeks. Information on PUSH scores and pressure ulcer sizes was presented in figures with no standard deviation data available. The figures showed no difference in mean PUSH scores (supplemented group: 13.2; control group: 14.0; P = 0.067 for between-group comparison) and ulcer sizes (supplemented group: 32.8 cm^2; control group: 32.8 cm^2; P = 0.76 for between-group comparison) between the two groups at week 4. The PUSH score was higher in the control group (14.6 ± 1.83) compared with the supplemented group (12.7 ± 3.6) at the start of the study. The pressure ulcer daily healing rate was higher in the control group (0.26 cm^2/day during the first two weeks and 0.27 cm^2/day during the subsequent two weeks) compared with the supplemented group (0.05 cm^2/day during the first two weeks and 0.12 cm^2/day during the subsequent two weeks).

Side effects

Miu 2021 assessed treatment-related side effects in the form of adverse gastrointestinal events. No events were found in either the amino acid-supplemented group or the standard diet group (Analysis 14.2; Appendix 16). We rated the evidence as low certainty and downgraded it by one level because of serious risk of bias (we rated risk of bias as some concerns) and by another level because of serious imprecision (the number of participants was low.)

None of the remaining prespecified review outcomes were reported.

Ornithine alpha-ketoglutarate compared with placebo (1 study)

Ulcer size

Meaume 2009 analyzed the effect of 10 g ornithine alpha-ketoglutarate daily on the healing of stage 2 or 3 heel pressure ulcers after accidental immobilization. Because of baseline imbalances in ulcer area in the two groups, the analysis was stratified by ulcer area. According to the study authors, there were no differences in wound area changes in the group with baseline pressure ulcer area more than 8 cm^2 (no data provided). In people with baseline pressure ulcer area of 8 cm^2 or less, there may be little to no difference in mean change in ulcer area between the ornithine alpha-ketoglutarate supplemented group and the placebo group, but the evidence is very uncertain (MD −0.60 cm^2; 95% CI −1.90 to 0.70; P = 0.36; very low-certainty evidence; Analysis 15.1; Appendix 17). Also, in this group with baseline pressure ulcer area of 8 cm^2 or less, there may be little to no difference with respect to the percentage change in ulcer area between the groups, but the evidence is very uncertain (MD −5.50%; 95% CI −34.04 to 23.04; P = 0.71; very low-certainty evidence; Analysis 15.2; Appendix 17). We downgraded the evidence for both outcomes to very low certainty; by one level due to serious risk of bias (we rated risk of bias as some concerns) and by two levels due to very serious imprecision (95% CI overlaps the no-effect line and a low number of participants).

Side effects

In Meaume 2009 there may be little to no difference in study-related side effects between the two groups, but the evidence is

very uncertain (ornithine group: 15/85 (17.65%); placebo group: 12/75 (16%); RR 1.10, 95% CI 0.55 to 2.20; P = 0.78; very low-certainty evidence; Analysis 15.3; Appendix 17). We downgraded the evidence by one level due to serious risk of bias (we rated risk of bias as some concerns) and by two levels due to very serious imprecision (95% CI overlaps the line of null effect and includes potential benefit and harm and a low number of participants and events).

None of the remaining prespecified review outcomes were reported.

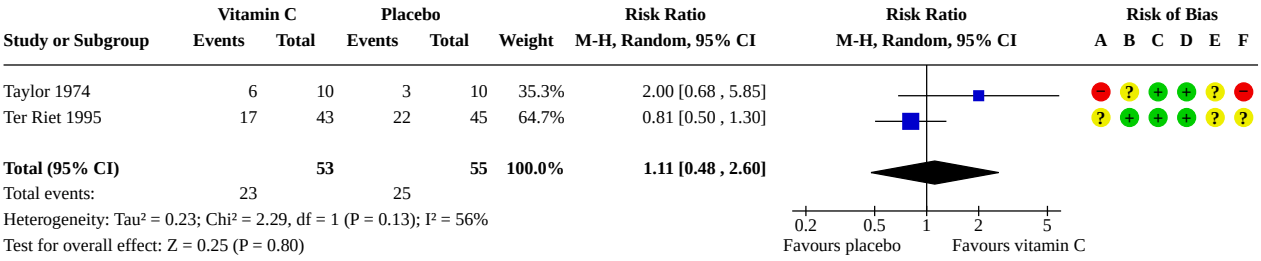
Vitamin C compared with placebo (2 studies)

Two studies investigated the effect of vitamin C (ascorbic acid) on pressure ulcer healing. Taylor 1974 followed up 20 people in surgical wards and reported data at one month. Ter Riet 1995 was intended to replicate Taylor 1974, with more participants (n = 88).

Pressure ulcers healed

Taylor 1974 reported that 6/10 (60%) participants in the ascorbic acid group had completely healed pressure ulcers compared with 3/10 (30%) participants in the placebo group. Ter Riet 1995 conducted an appropriate survival analysis to compare the overall risk of healing on ascorbic acid and placebo and found no difference between the groups (HR 0.78, 90% CI 0.44 to 1.39). In order to allow comparison and meta-analysis using this study, we extracted the data on the numbers of healed pressure ulcers from the survival curves of the study report. We pooled data using a random-effects model and found little to no difference between vitamin C and placebo on pressure ulcer healing, but the evidence is very uncertain (RR 1.11, 95% CI 0.48 to 2.60; P = 0.80, I^2 =56%; very low-certainty evidence; Analysis 16.1; Figure 17; Appendix 18). We downgraded the evidence by one level due to serious risk of bias (we rated one of the two studies as some concerns) and by two levels for very serious imprecision (95% CI overlaps the line of null effect and a low number of participants and events).

Figure 17. Comparison 16. Vitamin C versus placebo for pressure ulcer treatment, outcome 1: pressure ulcers healed



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Ulcer size

Taylor 1974 reported a greater mean reduction in pressure ulcer area in the group treated with vitamin C (84% reduction, SD 24.04) after one month compared with the placebo group (42.7% reduction, SD 23.43). The overall difference in means was 41.30% in favour of the vitamin C supplementation, but the evidence is very uncertain (95% CI −62.10 to −20.50; P < 0.0001; very low-certainty evidence; Analysis 16.2; Appendix 18). We downgraded the evidence by one level for serious risk of bias (we rated the study as high risk of bias) and by two levels for very serious imprecision (wide 95% CI and a low number of participants). Ter Riet 1995 reported that the mean volume reduction was 0 mL/week in the intervention group and 0.20 mL/week in the control group (difference −0.20 mL/week). The mean "clinical change", where improvements (i.e. surface reduction, healing velocity, volume reduction) were scored on a scale from −100% to +100%, was 17.89% per week in the intervention group and 26.08% per week in the control group (difference −8.19% per week).

None of the remaining prespecified review outcomes were reported.

Zinc sulphate compared with placebo (2 studies)

Pressure ulcers healed

Brewer 1967 compared zinc sulphate with placebo in 14 people with spinal cord injuries and poorly healing pressure ulcers. There may be little to no difference in healed pressure ulcers between the treatment group (83.33%) and the control group (57.14%), but the evidence is very uncertain (RR 1.46, 95% CI 0.70 to 3.04; P = 0.31; very low-certainty evidence; Analysis 17.1; Appendix 19). We downgraded the evidence by one level due to serious risk of bias (we rated the study as high risk of bias) and twice for very serious imprecision (95% CI overlaps the line of null effect and a low number of participants and events).

Ulcer size

Norris 1971 treated 18 people with pressure ulcers with either zinc sulphate supplements or a placebo. The zinc sulphate group

showed a mean reduction in pressure ulcer volume of 10.1 mL (SD 9 mL), whilst those in the placebo group showed a mean reduction in pressure ulcer volume of 6.0 mL (SD 17.5 mL). There may be little to no difference in the mean reduction of pressure ulcer volume between the group receiving zinc sulphate supplements and the placebo group, but the evidence is very uncertain (MD 4.10, 95% CI −9.25 to 17.45; P = 0.55; very low-certainty evidence; Analysis 17.2; Appendix 19). We downgraded the evidence by one level due to serious risk of bias (we rated the study as high risk of bias) and by two levels for very serious imprecision (95% CI overlaps the line of null effect and a low number of participants).

None of the remaining prespecified review outcomes were reported.

DISCUSSION

The studies of nutritional supplementation vary in terms of interventions, outcome measurements and follow-up; interpretation of these findings should be made with caution.

Summary of main results

Eleven studies compared six types of nutritional interventions for the prevention of pressure ulcers, with a combination of different macronutrients and micronutrients in different dosages and for a range of study periods. We performed two meta-analyses to compare the effect of energy, protein and micronutrient supplements and protein supplements with standard diets on pressure ulcer incidence. The analyses showed that these interventions may result in little to no difference in pressure ulcer incidence. It remains unclear whether other nutritional supplement compositions may reduce the risk of pressure ulcer development.

Twenty-four studies evaluated the effects of nutritional supplements on the healing of existing pressure ulcers. They used various outcome measures for pressure ulcer healing including the number of people with healed ulcers, changes in ulcer sizes/depth, and PUSH/DESIGN-R scores (as surrogate measures).

The meta-analyses showed that energy, protein and micronutrient supplements may slightly increase the number of healed pressure ulcers. Protein, arginine, zinc and antioxidant supplements as well as arginine and micronutrient supplements (2 studies) may slightly increase pressure ulcer healing, but have no effect on the number of healed pressure ulcers. The evidence is very uncertain about the effect of these supplements on side effects.

It is only with regard to one nutritional supplement that we are moderately confident about the evidence. Collagen supplements probably reduce the mean pressure ulcer area when compared to placebo. However, the evidence is very uncertain about the effect of this supplement on other pressure ulcer healing outcomes (e.g. PUSH scores) and on side effects. No study investigated the effects of collagen supplements on the number of healed pressure ulcers.

The evidence is very uncertain about the effect of vitamin C compared to placebo on the number of healed pressure ulcers.

The evidence is very uncertain about the effects of different doses of arginine; EPA, GLA and antioxidants; protein; specialized amino acid mixtures; ornithine alpha-ketoglutarate and zinc supplements on the number of healed pressure ulcers and pressure ulcer healing when compared to standard diet or placebo.

Overall completeness and applicability of evidence

Even though we included 33 studies in this review, the various combinations of different nutritional interventions, which were compared with a standard diet or a placebo, made it difficult to conclude which type of nutritional intervention may prevent or treat pressure ulcers. In addition, the included studies used different outcome measurements for pressure ulcer healing, and the suitability of the PUSH/DESIGN-R score as a surrogate measure of pressure ulcer healing is unclear. Regarding sample sizes, many studies included few participants and some had a considerable dropout rate. Furthermore, the follow-up time of some studies was short, making it unlikely that true effects of interventions would be detected. Some studies reported that laboratory markers of malnutrition improved during treatment, but the clinical effects of specific nutritional supplementation on the incidence of new ulcers or healing of existing ulcers were unclear.

Quality of the evidence

We rated certainty of the evidence for most of the outcomes as either very low or low because we judged overall risk of bias for most included studies as high or some concerns, with one or more risk of bias domains rated as high or some concerns. The other frequent reason for downgrading was imprecision.

Nearly half of the included studies were funded or supported by pharmaceutical companies, which raises concerns with regard to conflict of interest. Reporting bias cannot be ruled out in several of these studies, as often no protocol was published a priori. Therefore, interpretations and conclusions of the effects of the interventions should be considered with caution against the background of these findings.

Potential biases in the review process

Although we declared no conflict of interest, we were aware of the possibility of bias at every stage of the review process. In this review, we tried to minimize bias in several ways. Two review authors assessed the eligibility of the studies for inclusion, performed the data extraction and assessed the risk for bias, with each author working independently. For articles not written in English or understood by at least two review authors, the articles were either translated into English or assessed by external bilingual researchers (listed in the Acknowledgements). Although the RoB 2 tool, due to its specific questions, explanations and algorithms, allows for a more objective bias assessment than other tools, there still remains a certain degree of subjectivity in the bias assessment.

In industry-funded studies on nutrition interventions, there is a certain risk of publication bias due to not publishing non-significant studies. To reduce this bias, we screened all published study protocols and checked them for the publication of an original study. If none was found, we contacted the study authors and asked for information. Unfortunately, we were not able to locate all authors of published study protocols, or did not receive feedback from all of them (despite sending reminder emails). Due to the low number of studies for the respective interventions, it was not possible to check for a potential publication bias using funnel plots. The review authors declared no conflict of interest.

Agreements and disagreements with other studies or reviews

Different types of nutritional supplementation influence the rates of healing of different types of wounds in various ways (Daher 2022). Specifying the types of different nutritional supplementation when investigating the effect of nutritional supplementation on pressure ulcers is essential to make a clinically meaningful comparison and recommendation. Yet, most of the existing pressure ulcer prevention-related systematic reviews were rated as low-to-moderate quality when AMSTER was used to appraise the quality of systematic reviews (Yap 2021). These low-quality systematic reviews either combined different types of nutritional interventions and study designs in their analyses, or did not perform any risk of bias or heterogeneity assessments (Yap 2021).

Similarly, some pressure ulcer treatment-related systematic reviews combined different types of nutritional interventions in various modes of delivery to make clinical recommendations. For instance, a systematic review investigated the efficacy of zinc supplementation therapy in patients with pressure ulcers (Song 2020). However, Song 2020 combined data from studies using both topical zinc ointment and zinc-enriched oral supplements using meta-analysis and made recommendations for the use of zinc therapy in ulcer healing. Another systematic review investigated the efficacy of arginine-enriched formulas in pressure ulcer healing and concluded that arginine-enriched enteral nutrition supplements improved pressure ulcer healing (Liu 2017). However, Liu 2017 compiled data from RCTs with different types of arginine-enriched supplements on pressure ulcer treatment without meta-analysis. From what we found in this systematic review, the treatment effect of arginine varied depending on which other nutrients were provided along with it. Consequently, the effect of arginine on pressure ulcer healing remains unclear.

Another systematic review specifically investigated the wound healing effect of a protein and arginine-enriched micronutrient supplement on pressure ulcer healing using meta-analysis and found a similar treatment effect as in this systematic review (Cereda 2017). They used the former version of the Cochrane risk of bias tool for randomized studies (RoB 1; Higgins 2011), and rated all three included studies as low risk of bias (Cereda 2017). Consequently, Cereda 2017 recommended supporting the use of protein and arginine-enriched micronutrient supplements in pressure ulcer treatment. However, their recommendation should be interpreted with caution because there was inconsistency regarding the effect, and heterogeneity in the treatment effect shown in their meta-analysis, and they did not use GRADE to rate the quality of evidence. Also, two of the three studies included in their systematic review were conducted by their research team. In contrast, we used version 2 of the Cochrane risk of bias tool for randomized studies (RoB 2; Sterne 2019), and GRADE to rate the certainty of evidence, and found low-certainty evidence in the treatment effect of protein and arginine-enriched micronutrient supplements on ulcer healing.

With regard to the economic evaluation of nutritional interventions in pressure ulcer prevention and management, similar to what was found in Wong 2019, only a few of the nutritional interventions included an economic evaluation. It has to be noted that the treatment effect of nutritional interventions is still inconclusive and economic evaluations depend on the clinical efficacy of nutritional interventions (Wong 2019). Meta-analysis was not possible due to the heterogeneity of economic assessment methodologies and primary outcomes of the study designs (Wong 2019). High-quality and sufficiently powered studies investigating the clinical efficacy of specific nutritional supplementations in preventing and treating pressure ulcers are needed before considering economic evaluation.

AUTHORS' CONCLUSIONS

Implications for practice

Currently, there is no clear evidence that nutritional interventions reduce the development of pressure ulcers. Some nutritional supplement compositions (energy, protein and micronutrient supplements; protein, arginine, zinc and antioxidant supplements; arginine and micronutrient supplements and collagen supplements) are promising approaches to increasing pressure ulcer healing slightly. However, the underlying evidence is of low or very low certainty. Furthermore, we are unsure about the effect of these supplements on side effects and acceptability.

This conclusion should not be interpreted as proof that nutritional interventions have no or only little effect on pressure ulcer incidence or healing because the existing evidence base is of low to very low certainty. Moreover, people with or without pressure ulcers who are receiving health care and who are malnourished or at risk of malnutrition should receive expert nutritional assessment and interventions using specifically developed and validated national and international guidelines for diagnosing and treating malnutrition (risk).

Implications for research

Further research with larger numbers of patients and sound methodology is required to procure evidence for the impact of nutrition on pressure ulcers. Most of the included studies included malnourished patients, but data for malnourished individuals were not presented separately. It would be valuable to present separate data for malnourished and non-malnourished patients in future randomized controlled trials to enable subgroup analyses. For some supplements, there is preliminary evidence that they may contribute to the healing of pressure ulcers. The low confidence rating for these interventions was mainly due to a lack of precision. Studies with larger samples would provide more precise results and would probably increase confidence in the evidence for these supplements. Consideration should be given to constituents of the supplement and the method of application, as one study reported low tolerance of nasogastric tube feeding. No study investigated a special diet (e.g. high-protein or vegetarian diet) or dietary change. In order to save costs for supplements and to protect the climate (packaging waste), it would also be important to investigate more climate-friendly interventions in future research.

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Editorial contributions

Cochrane Wounds Group supported the authors in the development of this systematic review. The following people conducted the editorial process for this article.

Sign-off Editor (final editorial decision): Emma Sydenham, Cochrane Central Editorial Service; **Sign-off Editor** (first editorial decision) Martin Burton, Director of Cochrane UK Coordinating Editor of Cochrane ENT, University of Oxford, UK; **Managing Editor** (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Marwah Anas El-Wegoud, Cochrane Central Editorial Service; **Editorial Assistant** (conducted editorial policy checks and supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service; **Copy Editor** (copy editing and production): Denise Mitchell, Cochrane Central Production Service.

Peer-reviewers (provided comments and recommended an editorial decision)

Prof Declan Patton, RCSI University of Medicine and Health Sciences, declanpatton@rcsi.ie (**clinical review**); Prof. Dr. JMGA Schols, Dept. HSR, Maastricht University, The Netherlands (**clinical review**); Prof Michael Clark, Birmingham City University, UK (**clinical review**); Michela Piredda, RN, Associate Professor, Department of Medicine and Surgery, Research Unit of Nursing Science Campus Bio-Medico University of Roma (**clinical review**); Richard Simman, MD, FACS, FACCWS, Professor of Surgery, Department of Surgery, Division of Plastic Surgery, University of Toledo College of Medicine and Life Sciences Director of Wound Care at Jobst Vascular Institute ProMedica Health Network Toledo, Ohio (**clinical review**); Catherine Hofstetter (**consumer review**); Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (**methods review**); Anne Littlewood, Cochrane Oral Health (**search review**).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Anbar 2014

Study characteristics	
Methods	**Prevention study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 23 • Sample size (received intervention): 22 • Age, means (SD): 82.3 (6.1) • Male gender, No (%): 6 (27.3) • Female gender, No (%): 16 (72.7) • BMI, mean (SD) : 25.2 (3.2) • MNA, mean (SD): 24.8 (2.6) • At risk of malnutrition, No, (%): 8 (36.4) • MMSE mean; SD: 25.2 (4.9) Control group • Sample size (randomized): 28 • Sample size (received intervention): 28 • Age, means (SD): 83.7 (6.4) • Male gender, No (%): 11 (39.3) • Female gender, No (%): 17 (60,75) • BMI, mean (SD) : 24.7 (4.4) • MNA, mean (SD): 24.5 (2.9)

Anbar 2014 *(Continued)*

- At risk of malnutrition, No, (%): 10 (35.7)
- MMSE mean; SD: 23.7 (5.2)

Overall

- Female gender, No (%): 33 (66.0)
- At risk of malnutrition, No, (%): 18 (36.0)
- Male gender, No (%): 17 (34%)
- Sample size (randomized): 51
- Sample size (received intervention): 50

Included criteria: patients > 65 years who were admitted to the unit following hip fracture within 48 h of the injury and in whom orthopedic surgery was considered the treatment of choice.

Excluded criteria: presented to hospital > 48 h after the injury, receiving steroids and/or immunosuppression therapy; presence of active oncologic disease, multiple fractures, diagnosed dementia, required supplemental nasal oxygen which precludes the measurement of REE

Group differences: no significant or relevant differences detected

Interventions	**Intervention characteristics** Intervention: protein supplement • Type of diet/supplementation: usual hospital diet and ONS • Macronutrients and micronutrients: Ensure Plus (Abbott Lab-oratories) containing 355 kcal/237 mL and 13.5 g protein or Glucerna (Abbott Laboratories) containing 237 kcal/237 mL and 9.9 g protein/237 mL • Energy (kcal/kg/d): energy goal determined by repeated REE requirements • Amount of supplementation: up to the determined requirements • Mode of feeding: enteral • Intervention period (days): 24 h after surgery until either day 14 or at discharge (mean 10.1, SD 3.2) Control: standard diet • Type of diet/supplementation: usual hospital diet and a fixed dose of ONS if already prescribed • Energy (kcal/kg/d): hospital diets provide a mean of 1800 kcal and 80 g of protein in the event that the meals are completely eaten • Amount of supplementation: an individual prescription • Mode of feeding: enteral
Outcomes	New PUs • Outcome type: dichotomous outcome • Reporting: fully reported • Direction: lower is better • Data value: endpoint Length of hospital stay (days) • Outcome type: continuous outcome • Reporting: fully reported • Direction: lower is better • Data value: endpoint Gastrointestinal complications (adverse effects) • Outcome type: adverse event • Reporting: fully reported

Anbar 2014 *(Continued)*

- Data value: endpoint

Identification	**Sponsorship source:** Rabin Medical Center **Country:** Israel **Setting:** hospital, ortho-geriatric unit of a geriatrics department **Authors:** Anbar, R., Beloosesky, Y., Cohen, J., Madar, Z., Weiss, A., Theilla, M., Koren Hakim, T., Frishman, S. & Singer, P. **Institution:** Department of General Intensive Care, Rabin Medical Center **Email:** psinger@clalit.org.il **Address:** Petah Tikva 49100, Israel
Notes	

Arias 2008

Study characteristics	
Methods	**Prevention study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): - • Sample size (received intervention): 264 • Age, means (SD): 61.99 (18.81) • Male gender, No (%): 168 (63.6) • Female gender, No (%): 96 (36.4) • Slightly undernourished or at risk according to SGA (%): 188 (71.8) • Severely undernourished according to SGA (%): 74 (28.2) Control group • Sample size (randomized): - • Sample size (received intervention): 273 • Age, means (SD): 58.81 (19.84) • Male gender, No (%): 169 (61.9) • Female gender, No (%): 104 (38.1) • Slightly undernourished or at risk according to SGA (%): 211 (77.9) • Severely undernourished according to SGA (%): 60 (22.1) Overall • Male gender, No (%): 337 (62.8) • Female gender, No (%): 200 (37.2) • Slightly undernourished or at risk according to SGA (%): 399 (74.9) • Severely undernourished according to SGA (%: 134 (25.1) • Sample size (randomized): 667

Arias 2008 *(Continued)*

	• Sample size (received intervention): 537 **Included criteria:** mildly or seriously malnourished or at risk of being malnourished inpatients according to the SGA **Excluded criteria:** patients with diabetes, patients with decompensated liver disease with hepatic encephalopathy, impaired consciousness, and those who had difficulty understanding instructions and/or were disabled and had no collaborating family member **Group differences:** no significant differences between the groups (but only age, gender and nutritional status mentioned)
Interventions	**Intervention characteristics** Intervention: mixed nutritional supplements (high energy, high protein and micronutrients) • Type of diet/supplementation: standard hospital diet plus ONS • Macronutrients and micronutrients: oral supplement with 100 kcal/100 mL; 14.0% protein; 31.5% fat; 54.5% carbohydrate • Energy (kcal/kg/d): addition of up to 700 kcal • Amount of supplementation: up to 700 mL/d • Mode of feeding: enteral • Intervention period (days): until discharge, mean 17.2 (14.6) Control: standard diet • Type of diet/supplementation: standand hospital diet • Macronutrients and micronutrients: standard hospital diet • Energy (kcal/kg/d): - • Amount of supplementation: none • Mode of feeding: enteral • Intervention period (days): until discharge, mean 16.6 (13.0)
Outcomes	Proportion of participants who developed new PUs • Outcome type: dichotomous outcome • Reporting: fully reported • Data value: endpoint Occurrence of complications (PU, urinary infection, respiratory infection, catheter infection) • Outcome type: dichotomous outcome • Reporting: fully reported • Data value: endpoint Length of hospitalization (days) • Outcome type: continuous outcome • Reporting: fully reported • Data value: endpoint Mortality • Outcome type: dichotomous outcome • Data value: endpoint
Identification	**Sponsorship source:** no information **Country:** Uruguay **Setting:** hospital

Arias 2008 *(Continued)*

Authors: Arias S., Bruzzone I., Blanco V., Inchausti M., Garcia F., Casavieja G., Silveira, R., Ruiz Díaz, M.E., Belmonte. yS.

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Notes	

Banks 2016

Study characteristics	
Methods	**Treatment study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 25 • Sample size (received intervention): 24 • Age, means (SD): 62.3 (20.7) • Female gender, No (%): 11 (44) • BMI, mean (SD): 27.1 (8.4) • Weight means (SD) in kg: 79.2 (23.3) • Severe malnutrition measured with SGA, No (%): 7 (28) • Mild/moderate malnutrition measured with SGA, No (%): 13 (52) • Stage 2 of primary PU, No (%): 12 (48) • Stage 3 of primary PU, No (%): 8 (32) • Stage 4 of primary PU, (%): 5 (20) • PUSH score 0-5, No. (%): 4 (16) • PUSH score 6-11, No. (%): 16 (64) • PUSH score 12-17, No. (%): 5 (20) • PUSH score, median (range): 9 (5–14) • PUSH area, median (range), cm^2: 2.9 (1–2.9) Control group • Sample size (randomized): 25 • Sample size (received intervention): 25 • Age, means (SD): 65.8 (15.8) • Female gender, No (%): 6 (24) • BMI, mean (SD): 23.5 (4.4) • Weight means (SD) in kg: 70.7 (15.3) • Severe malnutrition measured with SGA, No (%): 6 (24) • Mild/moderate malnutrition measured with SGA, No (%): 15 (60) • Stage 2 of primary PU, No (%): 11 (44) • Stage 3 of primary PU, No (%): 7 (28) • Stage 4 of primary PU, No (%): 7 (28)

Banks 2016 *(Continued)*

- PUSH score 0-5, No. (%): 3 (12)
- PUSH score 6-11, No. (%): 17 (68)
- PUSH score 12-17, No. (%): 5 (20)
- PUSH score, median (range): 7 (4–17)
- PUSH area, median (range), cm^2: 1.5 (0.2–65.3)

Included criteria: PU stage 2-4 pre-existent at admission or acquired during admission

Excluded criteria: unable to receive nutrition support via the enteral route (on parenteral nutrition), inappropriate for intensive nutrition support (patients receiving palliative care or medically deteriorating), unable to follow nutrition support advice (cognitively impaired, language barriers), previously enrolled in the study

Group differences: more participants with a very high BMI (> 30) in intervention group (6 vs 1), more people can reposition and can walk in intervention group (7 vs 3), median PU area (cm^2) higher in intervention group (2.9 vs 1.5). Significantly more participants in the intervention group were already receiving a high-protein/energy diet as part of their standard care (17 vs 10)

Interventions	**Intervention characteristics** Intervention: mixed nutritional supplements (arginine, zinc and antioxidants) • Type of diet/supplementation: diet and/or supplements and a nutritional formula • Macronutrients and micronutrients: individually composed to meet estimated nutritional requirements of 1.2 g protein/kg body weight/day and the prescription of a 'wound healing' nutritional formula, enriched with arginine, vitamin C and zinc • Energy (kcal/kg/d): individually composed to meet 30 kcal/kg per day (5 participants met required energy) • Mode of feeding: enteral (both oral and tube) • Intervention period (days): during hospital stay until discharge • Nutritional care provided by: a research dietitian Control: standard diet • Type of diet/supplementation: diet and/or supplements • Macronutrients and micronutrients: standard hospital diet or high-protein/energy diet and/or nutritional supplements and/or enteral tube feeding • Energy (kcal/kg/d): energy intake similar to Iintervention group • Nutritional care provided by: provided by the clinical team which usually included a dietitian
Outcomes	PU healing (PUSH tool score) • Outcome type: continuous outcome • Scale: PUSH • Direction: lower is better • Data value: change from baseline PU healing (PUSH) % • Outcome type: continuous outcome • Direction: lower is better • Data value: change from baseline PU area change (cm^2) • Outcome type: continuous outcome • Direction: lower is better • Data value: change from baseline PU area change (%)

Banks 2016 *(Continued)*

- Outcome type: continuous outcome
- Direction: lower is better
- Data value: change from baseline

Median length of hospitalization (days)

- Outcome type: continuous outcome
- Direction: lower is better

Adverse effect (worsening PU)

- Outcome type: adverse event
- Data value: change from baseline

Adherence to the PU healing supplement prescription

- Outcome type: dichotomous outcome
- Direction: higher is better
- Data value: change from baseline

Non-adherence because of disliking the supplements

- Outcome type: dichotomous outcome
- Direction: lower is better
- Data value: endpoint

Non-adherence due to gastrointestinal side effects, including nausea and diarrhoea

- Outcome type: dichotomous outcome
- Direction: lower is better
- Data value: endpoint

Identification	**Sponsorship source:** Grant from the Queensland Health, Health Practitioner Research Scheme **Country:** Australia **Setting:** tertiary referral hospital **Authors:** Banks M.D., Ross L.J., Webster J., Mudge A., Stankiewicz M., Dwyer K., Coleman K., Campbell J. **Institution:** Department of Nutrition & Dietetics, Royal Brisbane & Women's Hospital **Email:** merrilyn.banks@health.qld.gov.au **Address:** Herston, Queensland, Australia
Notes	54% of participants in the intervention and 72% of participants in the control group reveived high-protein energy diet at day 10. Difference in the intervention is more who delivered it (clinicans versus dietitians)

Benati 2001

Study characteristics	
Methods	**Treatment study** **Study design:** RCT

Benati 2001 *(Continued)*

	Study grouping: parallel group
Participants	**Baseline characteristics** Intervention group 1 • Sample size (randomized and received intervention): 5 • Age (range): - • Male gender, No (%): 4 (80) • Female gender, No (%): 1 (20) Intervention group 2 • Sample size (randomized and received intervention): 5 • Age (range): - • Male gender, No (%): 3 (60) • Female gender, No (%): 2 (40) Control group • Sample size (randomized and received intervention): 6 • Age (range): - • Female gender, No (%): 4 (66.6) • Male gender, No (%): 2 (33.3) Overall • Sample size (randomized and received intervention): 16 • Age (range): 72-91 years • Male gender, No (%): 9 (56.25) • Female gender, No (%): 7 (43.75) • Katz activities of daily living score (range): 0- 3 **Included criteria:** hospital patients with (1) severe cognitive impairment (MMSE < 16), (2) reduced oral food intake and (3) PUs **Excluded criteria:** patients who were unlikely to benefit from nutritional supplementation **Group differences:** control group had more men than women, whilst one of the treatment groups had more women than men. **Additional PU prevention:** all participants laid on an alternating pressure air mattress. Pressure injury treatment was standardized with advanced protocols
Interventions	**Intervention characteristics** Intervention 1: protein supplement • Type of diet: supplement • Macronutrients and micronutrients of supplement: 37 g proteins/d • Energy (kcal/d): 500 Kcal extra/d • Amount of supplementation: 2 times/d, each 200 mL • Intervention period (days): 14 • Mode of feeding: enteral Intervention 2: mixed nutritional supplements (protein, arginine, zinc and antioxidants) • Type of diet: supplement • Macronutrients and micronutrients of supplement: 37 g proteins, 7.5 g arginine and 25mg zinc/d as well as antioxidants

Benati 2001 *(Continued)*

- Energy (kcal/d): 500 Kcal extra/d
- Amount of supplementation: 2 times/d, each 200 mL
- Intervention period (days): 14
- Mode of feeding: enteral

Control: standard diet

- Type of diet: normal hospital diet
- Energy (kcal/d): unclear
- Mode of feeding: enteral

Outcomes	PU healing • Outcome type: continuous outcome • Reporting: not reported • Scale: PSST • Range: 13-65 • Unit of measure: points • Direction: lower is better • Data value: change from baseline Notes: individual patient scores at each time point (day 0, day 5, day 10 and day 16) presented in a figure, no mean group scores reported
Identification	**Sponsorship source:** not reported **Country:** Italy **Setting:** hospital, Department of Geriatric Medicine **Authors:** Benati G., Delvecchio S., Cilla D., Pedone V. **Institution:** Department of Geriatric Medicine, Morgagni-Pierantoni Hospital **Email:** - **Address:** Viale Forlanini, 37, 1-47100 Forli, Italy
Notes	

Botella Carretero 2008

Study characteristics	
Methods	**Prevention study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group 1 • Sample size: 30 • Female gender, No (%): 27 (90) • Male gender, No (%): 3 (10) • Age, mean (SD), years: 83.1 (6.3)

Botella Carretero 2008 *(Continued)*

- BMI, mean (SD): 24.2 (3.0)
- MNA score points, mean (SD): 18.7 (4.2)
- No malnutrition (no significant weight loss and normal serum albumin concentrations), No (%): 15 (50)

Intervention group 2

- Sample size: 30
- Female gender, No (%): 21 (70)
- Male gender, No (%): 9 (30)
- Age, mean (SD), years: 84.6 (5.7)
- BMI, mean (SD): 23.7 (3.5)
- MNA score points, mean (SD): 20.5 (2.9)
- No malnutrition (no significant weight loss and normal serum albumin concentrations), No (%): 16 (53.3)

Control group

- Sample size: 30
- Female gender, No (%): 23 (76.7)
- Male gender, No (%): 7 (23.3)
- Age, mean (SD), years: 83.7 (7.9)
- BMI, mean (SD): 23.6 (2.4)
- MNA score points, mean (SD): 19.4 (3.6)
- No malnutrition (no significant weight loss and normal serum albumin concentrations), No (%): 19 (63.3)

Overall

- Sample size: 90
- Female gender, No (%): 71 (78.9)
- Male gender, No (%): 19 (21.1)
- No malnutrition (no significant weight loss and normal serum albumin concentrations), No (%): 60 (66.7)

Included criteria: patients > 65 years, admitted to hospital because of a hip fracture, and orthopedic surgery was considered as treatment, normally nourished or only mildly undernourished geriatric patients

Excluded criteria: patients with moderate or severe malnutrition (weight loss of > 5% in the previous month or > 10% in the previous 6 months from their usual weight and/or serum albumin concentrations < 2.7 g/dL), acute and/or chronic renal failure, hepatic insufficiency or cirrhosis (Child B or C), severe heart failure, respiratory failure, any gastrointestinal condition that may preclude the patient from adequate oral nutrition intake, ONS in the previous 6 months

Group differences: no relevant or significant group differences. Slightly more participants without malnutrition in the control group, but hardly any differences in mean BMI or weight

Interventions	**Intervention characteristics** Intervention 1: protein supplement • Type of diet/supplementation: protein powder dissolved in water or in the diet's milk or soup • Macronutrients and micronutrients: commercial protein powder (Vegenat-med Proteina; Vegenat SA, Badajoz, Spain; 10-g packets, with each providing 9 g of protein and 38 kcal) to aim at 36 g of protein/d • Energy (kcal/kg/d): 4 packets/d, 38 kcal each • Amount of supplementation: 4 packets/d • Mode of feeding: enteral

Botella Carretero 2008 *(Continued)*

- Intervention period: 48 h after operation until hospital discharge

Intervention 2: high-protein, high-energy supplement

- Type of diet/supplementation: bars to eat/drink
- Macronutrients and micronutrients: commercial enteral nutrition for oral intake (Resource Hiperproteico; Novartis Medical Nutrition, Barcelona,Spain); 200-mL bricks, with each providing 18.8 g of protein and 250 kcal) to aim at 37.6 g of protein and 500 kcal/d
- Energy (kcal/kg/d): 2 bricks/d, 250 kcal each
- Amount of supplementation: 2 x 200 mL bricks
- Mode of feeding: enteral
- Intervention period: 48 h after operation until hospital discharge

Control: standard diet

- Type of diet/supplementation: normal hospital diet, no supplements
- Macronutrients and micronutrients: -
- Energy (kcal/kg/d): -
- Mode of feeding: enteral
- Intervention period: during hospital stay

Outcomes	New PUs • Outcome type: dichotomous outcome • Data value: change from baseline Adverse effects (vomiting and diarrhoea) • Outcome type: dichotomous outcome • Data value: change from baseline Length of hospital stay (days) • Outcome type: continuous outcome • Data value: endpoint • Notes: presented in figure Adverse events (postoperative complication rate) • Outcome type: dichotomous outcome • Data value: endpoint Adherence to ONS (mean investigated amount of prescribed supplement), % • Outcome type: continuous outcome • Data value: endpoint
Identification	**Sponsorship source:** José I. Botella-Carretero was supported by the Fundación para la Investigación Biomédica, Hospital Ramón y Cajal, Madrid, Spain **Country:** Spain **Setting:** hospital **Authors:** Botella-Carretero, J.I., Iglesias, B., Balsa, J.A., Zamarrón, I., Arrieta, F., Vázquez C. **Institution:** Unit of Clinical Nutrition and Dietetics, Department of Endocrinologyand Nutrition, Hospital Ramón y Cajal **Email:** jbotella.hrc@salud.madrid.org

Botella Carretero 2008 *(Continued)*

	Address: Carretera de ColmenarKm 9.1, 28034 Madrid, Spain
Notes	

Bourdel Marchasson 2000

Study characteristics	
Methods	**Prevention study** **Study design:** RCT **Study grouping:** parallel group **Randomization methods:** 19 wards (54%) were selected and stratified according to their speciality and their recruitment for elderly patients with PU risk factors. The ward specialities were neurology, gastroenterology, orthopedic and vascular surgery, internal medicine, and geriatric medicine. These wards were then randomized into groups according to the nutritional intervention
Participants	**Baseline characteristics** Intervention group • Sample size: 295 • Age, means (SD) intervention group/control group: 83.6 (7.3) • Female gender, No (%) intervention group/control group: 199 (67.5) • Male gender, No (%): 96 (32.5) • Weight (kg), mean (SD): 60.2 (17.8) • Norton score 5–10 (high PU risk) (%): 84 (28.5) • Care dependency (Kuntzmann score), mean (SD): 8.2 (1.4) Control group • Sample size: 377 • Age, means (SD) IG/KG: 83.0 (7.1) • Female gender, No (%) IG/KG: 238 (63.1) • Male gender, No (%): 139 (36.9) • Weight (kg), mean (SD): 55.2 (15.0) • Norton score 5–10 (great PU risk) (%): 130 (34.5) • Care dependency (Kuntzmann score), mean (SD): 8.4 (1.3) Overall • Sample size: 672 **Included criteria:** patients > 65 years in the acute phase of a critical illness, unable to move by themselves, and unable to eat independently at admission **Excluded criteria:** patients with PUs at admission were excluded. **Group differences:** intervention group included more participants with stroke, heart failure, and dyspnoea, and fewer with antecedent falls, delirium, lower limb fractures and digestive disease. Furthermore, the nutritional intervention group had a significantly lower risk of developing PUs (Norton score) but was significantly less dependent (Kuntzman score) and had a lower serum albumin. **Additional PU prevention:** both groups underwent the same PU prevention programme given to at-risk patients: changing positions, special mattresses, and cleaning care.

Bourdel Marchasson 2000 *(Continued)*

Interventions	**Intervention characteristics** Intervention: mixed nutritional supplements (high energy, high protein and micronutrients) • Type of diet/supplementation: ONS • Macronutrients and micronutrients: standard diet plus 2 ONS/d: 30% protein; 20% fat; 50% carbohydrate; minerals and vitamins, such as 1.8 mg zinc and 15 mg vitamin C • Energy (kcal/kg/d): standard diet (1800 kcal/d) plus ONS (400 kcal per day) • Amount of supplementation: 2 supplements/d each 200 mL, 1 with breakfastand the other in mid-afternoon • Mode of feeding: enteral • Intervention period: 15 days or until discharge (if participants stayed fewer than 15 days) Control: standard diet • Type of diet/supplementation: standard diet • Macronutrients and micronutrients: - • Energy (kcal/kg/d): 1800kcal/d in 3 meals • Mode of feeding: enteral • Intervention period (days): -
Outcomes	New PUs • Outcome type: dichotomous outcome • Reporting: fully reported • Data value: endpoint Adverse events (deaths) • Outcome type: dichotomous outcome • Reporting: fully reported • Data value: endpoint
Identification	**Sponsorship source:** Projet Hospitalier de Recherche Clinique, Ministere de la Sante et de l'Action Humanitaire, Direction Generale de la Sante, and the Direction des Hospitaux **Country:** France **Setting:** hospitals, multicenter **Authors:** Bourdel-Marchasson, I., Barateau, M., Rondeau V, Dequae-Merchadou, L., Salles-Montaudon, N., Emeriau, J.P., Manciet, G., Dartigues, J.F. **Institution:** Centre de Geriatrie du Centre Hospitalo-Universitaire de Bordeaux **Email:** isabelle.bourdel-marchasson@chu-aquitaine.f **Address:** Centre de Geriatrie du Centre Hospitalo-Universitaire de Bordeaux, Hoˆ pital Xavier-Arnozan, 33604 Pessac, France
Notes	

Brewer 1967

Study characteristics	
Methods	**Treatment study**

Brewer 1967 *(Continued)*

	Study design: RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size: 7 Control group • Sample size: 7 **Included criteria:** 14 spinal cord injured patients with poor healing decubitus ulcers of various sizes, types, locations, and duration (5 months to over 2 years). No further description available **Excluded criteria:** no information **Group differences:** unclear
Interventions	Intervention: zinc sulphate • Type of diet/supplementation: capsule of zinc sulphate • Macronutrients and micronutrients: 50 mg zinc • Amount of supplementation: 1 capsule daily (220 mg; 50 mg zinc) • Mode of feeding: enteral • Intervention period: no information Control: placebo • Type of diet/supplementation: placebo capsule • Macronutrients and micronutrients: lactose • Amount of supplementation: 1 capsule daily • Mode of feeding: enteral • Intervention period: no information
Outcomes	PU healing • Outcome type: dichotomous outcome Serum and urinary zinc increase after 2-3 months • Outcome type: continuous outcome • Reporting: not reported
Identification	**Sponsorship source:** no information provided **Country:** unclear **Setting:** unclear **Authors:** Brewer R.D. **Institution:** no information provided **Email:** no information provided **Address:** no information provided
Notes	Setting and country not clearly described. Author was chief of the 'Spinal Cord Injury Service', Hines, Illinois, United States.

Cereda 2009

Study characteristics	
Methods	**Treatment study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 15 • Sample size (received intervention): 13 • Age, mean (SD), years: 82.1 (9.6) • Male gender, No (%): 4 (30.8) • Female gender, No (%): 9 (69.2) • MMSE, mean (SD): 7 (53.8) • BMI, mean (SD): 20.8 (3.2) • Geriatric Nutritional Risk Index, mean (SD): 81.4 (11.9) • Norton Index, mean (SD): 6.8 (1.6) • PU stage 2, No (%): 2 (15.4) • PU stage 3, No (%): 4 (30.8) • PU stage 4, No (%): 7 (53.8) • PU location: sacrum, No (%): 5 (38.5) • PU location: foot, No (%): 4 (30.8) • PU location: ankle, No (%): 4 (30.8) Control group • Sample size (randomized): 15 • Sample size (received intervention): 15 • Age, mean (SD), years: 81.4 (9.9) • Male gender, No (%): 6 (40.0) • Female gender, No (%): 9 (60.0) • MMSE, mean (SD): 7 (46.7) • BMI, mean (SD): 23.1 (5.0) • Geriatric Nutritional Risk Index, mean (SD): 80.8 (9.3) • Norton Index, mean (SD): 8.7 (4.0) • PU stage 2, No (%): 3 (20.0) • PU stage 3, No (%): 4 (26.7) • PU stage 4, No (%): 8 (53.3) • PU location: sacrum, No (%): 8 (53.3) • PU location: back, No (%): 1 (6.7) • PU location: foot, No (%): 3 (20.0) • PU location: ankle, No (%): 3 (20.0) Overall • Sample size (randomized): 30 • Sample size (received intervention): 28 • Male gender, No (%): 10 (35.7) • Female gender, No (%): 18 (64.3)

Cereda 2009 *(Continued)*

- MMSE, mean (SD): 14 (50.0)
- PU stage 2, No (%): 5 (17.9)
- PU stage 3, No (%): 8 (28.6)
- PU stage 4, No (%): 15 (53.4)
- PU location: sacrum, No (%): 13 (46.4)
- PU location: back, No (%): 1 (3.6)
- PU location: foot, No (%): 7 (25.0)
- PU location: ankle, No (%): 7 (25.0)

Included criteria: residents of long-term care aged ≥ 65 admitted to 4 different facilities, PU stage 2, 3, or 4 lesions as assessed according to the revised (2007) NPUAP staging system. Patients fed orally and through feeding tubes.

Excluded criteria: presence of acute illness (e.g, infection) or chronic disease (e.g. diabetes mellitus, peripheral vascular disease, autoimmune or neoplastic disorders) possibly affecting the nutritional intervention and healing process, positive culture from PU swab sampling, use of immunosuppressive therapies, development of the lesion > 1 month before evaluation, and lack of dietary adherence.

Group differences: participants in the experimental group had a lower BMI.

Interventions	**Intervention characteristics** Intervention: mixed nutritional supplements (protein, arginine, zinc and antioxidants) • Type of diets/supplementation: high-energy, high-protein supplementation with arginine, zinc and vitamin C • Macronutrients and micronutrients: for the oral-fed formula (Cubitan, Nutricia, Milan,Italy): 34 g protein, 6 g arginine, 500 mg vitamin C, and 18 mg zinc; for the tube-fed formula: high-protein formula (20% energy from protein; Cubison, Nutricia) enriched with arginine, zinc, and vitamin C (in 100 mL: 100 kcal, 5.5 g protein, 0.85 g arginine, 38 mg vitamin C, and 2 mg zinc) • Additional energy: the oral-fed formula provided a total of 500 kcal • Amount of supplementation: 2 bottles with 400 mL for oral-fed; 1000 mL for the tube-fed were infused together with appropriate volumes of an isocaloric standard formula • Mode of feeding: enteral • Intervention period (days): 56 Control: standard diet • Type of diets/supplementation: a standard hospital diet for oral-fed/standard formula for tube-fed • Macronutrients and micronutrients: 16% energy from protein • Amount of supplementation: none • Mode of feeding: enteral • Intervention period (days): 56
Outcomes	PU area (mm^2) • Outcome type: continuous outcome • Direction: lower is better • Data value: change from baseline PUSH • Outcome type: continuous outcome • Direction: lower is better • Data value: change from baseline PU infections, %

Cereda 2009 *(Continued)*

- Outcome type: adverse event
- Direction: lower is better

Days of antibiotic therapy

- Outcome type: continuous outcome
- Direction: lower is better
- Data value: endpoint

Complete healing

- Outcome type: dichotomous outcome
- Direction: higher is better
- Data value: endpoint

Identification	**Sponsorship source:** Nutricia (Milan, Italy) provided the supplements **Country:** Italy **Setting:** long-term care (4 long-term care facilities) **Authors:** Cereda, E., Gini, A., Pedrolli, C., Vanotti, A. **Institution:** International Center for the Assessment of Nutritional Status, University of Milan **Email:** emanuele.cereda@virgilio.it **Address:** Manuele Cereda, International Center for the Assessment of Nutritional Status (ICANS), University of Milan, via Botticelli 21, 20133 Milan, Italy.
Notes	No conflict of interest stated

Cereda 2015

Study characteristics	
Methods	**Treatment study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 101 • Sample size (received intervention): 101 • Male gender, No (%): 32 (31.7) • Female gender, No (%): 69 (68.3) • Age mean (SD): 81.1 (10.8) • Long-term care, No (%): 64 (63.4) • Dementia diagnosis, No (%): 54 (53.5) • PU sacrum, No (%): 65 (64.3) • PU heel, No (%): 14 (13.9) • Mean Braden Scale score (SD): 11.2 (3.9) • Mean BMI (SD): 20.2 (3.6) • PU stage 2, No (%): 27 (26.7)

Cereda 2015 *(Continued)*

- PU stage 3, No (%): 28 (27.7)
- PU stage 4, No (%): 46 (45.5)
- Low BMI (< 20 kg/m^2 and < 21 kg/m^2 for patients aged < 65 and ≥ 65 years), No (%): 72 (71.3)
- Unintentional weight loss (≥ 10% of body weight in 3 months or ≥ 5% in 1 month), No (%): 71 (70.3)

Control group

- Sample size (randomized): 99
- Sample size (received intervention): 99
- Male gender, No (%): 31 (31.3)
- Female gender, No (%): 68 (68.7)
- Age mean (SD): 81.7 (10.7)
- Long-term care, No (%): 68 (68.7)
- Dementia diagnosis, No (%): 53 (53.5)
- PU sacrum, No (%): 63 (63.6)
- PU heel, No (%): 13 (13.1)
- Mean Braden Scale score (SD): 11.8 (3.5)
- Mean BMI (SD): 21.2 (3.8)
- PU stage 2, No (%): 34 (34.3)
- PU stage 3, No (%): 31 (31.3)
- PU stage 4, No (%): 34 (34.3)
- Low BMI (< 20 kg/m^2 and < 21 kg/m^2 for patients aged < 65 and ≥ 65 years), No (%): 67 (67.7)
- Unintentional weight loss (≥ 10% of body weight in 3 months or ≥ 5% in 1 month), No (%): 71 (71.7)

Overall

- Sample size (randomized): 200
- Sample size (received intervention): 200
- Female gender, No (%): 137 (68.5)
- Male gender, No (%): 63 (31.5)
- Long-term care, No (%): 132 (66)
- Dementia diagnosis, No (%): 107 (53.5)
- PU sacrum, No (%): 128 (64.0)
- PU heel, No (%): 27 (13.5)

Included criteria: adult, malnourished long-term care residents or patients receiving home-care services with PU stage 2, 3, or 4, who were able to drink oral nutritional supplements and provide written informed consent

Excluded criteria: poorly controlled diabetes, acute organ failure, advanced renal or hepatic insufficiency, moderate to severe heart failure, chronic obstructive pulmonary disease or peripheral vascular disease, connective tissue disease, previous or current neoplastic disease, haemoglobin level < 10 g/dL, obesity, current immunosuppressive therapy, infected PU, cellulitis, sepsis, osteomyelitis, type of artificial nutrition

Group differences: experimental group fewer participants in long-tem care (63.4% vs 68.7%), more primary PUs at stage 4 (45.5% vs. 34.3%), more multiple PUs (49.5% vs. 41.4%), more participants with low BMI (71.3% vs 67.7%), more participants with a reduced energy intake

Sites: 7 sites (long-term care and home care)

Interventions	**Intervention characteristics** Intervention: mixed nutritional supplements (arginine, zinc and antioxidants) • Type of diet/supplementation: oral formula

Cereda 2015 *(Continued)*

- Macronutrients and micronutrients: formula (Cubitan) enriched with arginine, zinc and antioxidant oligo elements (for 100 mL: 10 g proteins, arginine 1.5 g, zinc 4.5 mg, copper 675 mcg, manganese 1.3 mg, vitamin E (a-tocopherol) 19.0 mg)
- Amount of supplemention: 2 bottles/d (400 mL)
- Additional energy: 500 kilocalories/d
- Mode of feeding: enteral
- Intervention period: 8 weeks (or until complete healing)

Control: placebo (Isocaloric oral formula)

- Type of diet/supplementation: placebo formula
- Macronutrients and micronutrients: isonitrogenous isocaloric oral formula (for 100 mL: arginine no addition, zinc 2.3 mg, copper 338 mcg, manganese 0.63 mg, vitamin E (a-tocopherol) 2.3 mg)
- Amount of supplemention: 2 bottles/d (400 mL)
- Additional energy: 500 kilocalories/d
- Mode of feeding: enteral
- Intervention period: 8 weeks (or until complete healing)

Outcomes

Mean reduction in PU area (%)

- Outcome type: continuous outcome
- Reporting: fully reported
- Scale: Visitrak wound measurement system
- Unit of measure: percent
- Direction: lower is better
- Data value: change from baseline

≥ 40% reduction in PU area at 8 weeks

- Outcome type: dichotomous outcome
- Reporting: fully reported
- Scale: Visitrak wound measurement system
- Unit of measure: percent
- Direction: lower is better
- Data value: endpoint

Complete healing, %

- Outcome type: dichotomous outcome
- Reporting: fully reported
- Scale: Visitrak wound measurement system
- Direction: higher is better
- Data value: endpoint

PU infections, %

- Outcome type: dichotomous outcome
- Reporting: fully reported
- Direction: lower is better
- Data value: endpoint

Mean number of dressings

- Outcome type: continuous outcome
- Direction: lower is better
- Data value: endpoint

Adverse effects (gastrointestinal intolerance)

Cereda 2015 *(Continued)*

- Outcome type: adverse event
- Reporting: fully reported
- Data value: endpoint

Adverse events (deaths)

- Outcome type: adverse event
- Reporting: fully reported
- Direction: lower is better

Adverse events (hospitalization)

- Outcome type: adverse event
- Reporting: fully reported
- Direction: lower is better

Costs of oral nutritional supplements (EUR)

- Outcome type: continuous outcome
- Reporting: partially reported
- Direction: lower is better
- Data value: endpoint

Non-nutritional costs in EUR (managment of PUs, dressing materials, antibiotics, mattress, tests)

- Outcome type: continuous outcome
- Direction: lower is better

Identification	**Sponsorship source:** Azienda Ospedaliera Universitaria Maggiore della Carita **Comments:** Cereda E. got grants and other from Nutricia Italia. Klersy C. got personal fees from Nutricia Italia during the conduct of the study. **Country:** Italy **Setting:** Long-term care and home-care services **Authors:** Cereda, E., Klersy, C., Serioli, M., Crespi, A., D'Andrea, F., for the OligoElement Sore Trial Study Group **Institution:** Servizio di Dietetica e Nutrizione Clinica, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo **Email:** e.cereda@smatteo.pv.it **Address:** Viale Golgi 19, 27100 Pavia, Italy
Notes	**Additional data used:** Cereda 2017 for outcomes according to cost-effectiveness

Chernoff 1990

Study characteristics	
Methods	**Treatment study** **Study design:** RCT **Study grouping:** parallel group

Chernoff 1990 *(Continued)*

Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 6 • Sample size (received intervention): 6 Control group • Sample size (randomized): 6 • Sample size (received intervention): 6 Overall • Sample size (randomized): 12 • Sample size (received intervention): 12 • Age, mean (SD), years: 71.5 (range: 65-88) • Male gender, N (%): 5 (41.7) • Female gender, N (%): 7 (58.3) **Included criteria:** tube-feeding, dependent patients with pressure ulcers **Excluded criteria:** not mentioned **Group differences:** no information
Interventions	Intervention: protein supplement • Type of diet/supplementation: very high-protein formula • Macronutrients and micronutrients: 25% calories from protein • Mode of feeding: enteral (tube feeding) • Intervention period (days): 56 Control group: standard diet • Type of diet/supplementation: high-protein formula • Macronutrients and micronutrients: 16% calories from protein • Mode of feeding: enteral (tube feeding) • Intervention period (days): 56
Outcomes	Complete healing • Outcome type: dichotomous outcome • Direction: higher is better • Data value: endpoint Mean reduction in ulcer area • Outcome type: continuous outcome • Reporting: fully reported • Direction: higher is better • Data value: endpoint
Identification	**Sponsorship source:** no information **Country:** USA **Setting**: unclear (institutionalized patient) **Authors:** Chernoff RS, Milton KY, Lipschitz DA

Chernoff 1990 *(Continued)*

Institution: Medical Center and Devision on Aging

Email: -

Address: Medical Center and Devision on Aging, Department of Medicine, University of Arkansas for Medical Scienes, Little Rock, Arkansas

Notes

Craig 1998

Study characteristics

Methods

Prevention study

Study design: RCT

Study grouping: parallel group

Participants

Baseline characteristics

Intervention group

- Sample size (randomized): 18
- Sample size (analyzed): 16
- Age, mean (SD), years: 82 (3.0)

Control group

- Sample size (randomized): 16
- Sample size (analyzed): 14
- Age, mean (SD), years: 80 (2.0)

Overall

- Sample size (randomized): 34
- Sample size (analyzed): 30

Included criteria: 34 patients ≥ 50 years old with a history of type 2 diabetes mellitus or had documented hyperglycaemia as evidenced by either a plasma glucose random measurement of > 200 mg/dL or a fasting plasma glucose > 140 mg/dL on 2 occasions; required total enteral nutrition support by tube; were able to tolerate a volume of formula that maintained body weight.

Excluded criteria: not mentioned

Group differences: according to the authors no significant differences between groups at baseline for age, weight, gender, race, height, or long-term care facility (no numbers presented). No information on presure ulcers.

Interventions

Intervention characteristics

Intervention: reduced carbohydrate, modified-fat formula

- Type of diet/supplementation: disease-specific formula (reduced carbohydrate, modified-fat)
- Macronutrients and micronutrients: Glucerna specialized nutrition with fibre for patients with abnormal glucose tolerance, per 1000 mL: 41.8 g protein, 93.7 g carbohydrate, 55.7 g fat
- Energy (kcal/kg/d): per 1000 mL: 1000 kcal
- Amount of supplementation: volume of feeding was based on individual requirements and established by standard procedures of the dietary and medical personnel

Craig 1998 *(Continued)*

	• Mode of feeding: enteral (tube feeding) • Intervention period: 3 months Control: standard high-carbohydrate formula • Type of diets/supplementation: standard high-carbohydrate formula • Macronutrients and micronutrients: Jevity isotonic liquid nutrition with fibre; per 1000 mL: 44.4 g protein, 151.7 g carbohydrate, 35.9 g fat • Energy (kcal/kg/d): per 1000 mL: 1060 kcal • Amount of supplementation: volume of feeding was based on individual requirements and established by standard procedures of the dietary and medical personnel • Mode of feeding: enteral (tube feeding) • Intervention period: 3 months
Outcomes	PUs experienced during study • Outcome type: dichotomous outcome • Reporting: fully reported • Direction: lower is better • Data value: endpoint Adverse events (deaths) • Outcome type: dichotomous outcome • Reporting: fully reported • Direction: lower is better • Data value: endpoint Adverse events (all infections) • Outcome type: dichotomous outcome • Direction: lower is better • Data value: endpoint
Identification	**Sponsorship source:** Research supported by Ross Products Division, Abbott Laboratories **Country:** USA **Setting:** long-term care facilities (2 facilities) **Authors:** Craig, LD., Nicholson, S., Silverstone, F.A., Kennedy, R.D. **Institution:** Beth Abraham Hospital **Email:** isa.craig@rossnutrition.com **Address:** 625 Cleveland Avenue, Columbus, OH 43215-1724, USA
Notes	

Dennis 2005

Study characteristics	
Methods	**Prevention study** **Study design:** RCT

Dennis 2005 *(Continued)*

	Study grouping: parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 2016 • Sample size (received intervention): 1937 • Age, mean (SD), years: 71 (12) • Male gender, No (%): 1071 (53) • Female gender, No (%): 945 (47) • Nutritional status (malnutrition), No (%): 156 (8) Control group • Sample size (randomized): 2007 • Sample size (received intervention): 1959 • Age, mean (SD), years: 71 (13) • Male gender, No (%): 1078 (54) • Female gender, No (%): 929 (46) • Nutritional status (malnutrition), No (%): 158 (8) Overall • Sample size (randomized): 4023 • Sample size (received intervention): 3896 • Male gender, No (%): 2149 (53) • Female gender, No (%): 1874 (47) • Nutritional status (malnutrition), No (%): 314 (8) **Included criteria:** patients admitted with a recent stroke (first or recurrent stroke no more than 7 days before admission) could be enrolled, if they passed their swallow screen, the responsible clinician was uncertain whether to use oral nutritional supplements, and the patient (or a relative) consented to enrolment. **Excluded criteria:** patients with subarachnoid haemorrhage were excluded. **Group differences:** none evident
Interventions	**Intervention characteristics** Intervention: protein supplement • Type of diet/supplementation: oral nutritional supplement and standard hospital diet • Macronutrients and micronutrients: oral protein energy supplements equivalent to 360 mL at 6.27 kJ/mL and 62.5 g/L in protein • Amount of supplementation: 360 mL/d • Mode of feeding: enteral • Intervention period: until discharge Control: standard diet • Type of diet/supplementation: standard hospital diet • Macronutrients and micronutrients: - • Mode of feeding: enteral • Intervention period: until discharge
Outcomes	New PUs

Dennis 2005 *(Continued)*

- Outcome type: dichotomous outcome

Quality of life (general health status)

- Outcome type: continuous outcome
- Reporting: fully reported
- Scale: EUROQoL
- Range: ranging from 0, death, to 1, perfect health

Adverse events (deaths)

- Outcome type: dichotomous outcome

Identification	**Sponsorship source:** Health Technology Assessment Board of NHS Research and Development in UK; the Stroke Association; the Chief Scientist Office of the Scottish Executive; Chest, Heart and Stroke Scotland; The Royal Australasian College of Physicians supported the trial in Hawkes Bay, New Zealand. **Country:** 15 countries: Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, Hong Kong, India, Italy, New Zealand, Poland, Portugal, Republic of Ireland, Turkey, UK **Setting:** hospitals (n = 125) **Authors:** Dennis M **Institution:** Department of Clinical Neurosciences, Western General Hospital, Edinburgh **Email:** martin.dennis@ed.ac.uk **Address:** Department of Clinical Neurosciences, Western General Hospital, Edinburgh EH4 2XU, UK
Notes	

Derossi 2009

Study characteristics	
Methods	**Prevention study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 54 • Sample size (received intervention): 54 • Age, mean (SD), years: 79.9 (7.3) • Male gender, No (%): 9 (16.6) • Female gender, No (%): 45 (83.3) • Dementia diagnosis, No (%): 5 (9) • BMI, mean (SD): 23.3 (5.1) • Nutritional status, BMI 18-28, No (%): 39 (72) • Nutritional status, BMI > 28, No (%): 10 (19) Control group

Derossi 2009 *(Continued)*

- Sample size (randomized): 53
- Sample size (received intervention): 53
- Age, mean (SD), years: 80.4 (6.8)
- Male gender, No (%): 8 (15.0)
- Female gender, No (%): 45 (84.9)
- Dementia diagnosis, No (%): 7 (13)
- BMI, mean (SD): 21.8 (4.9)
- Nutritional status, BMI 18-28, No (%): 35 (66)
- Nutritional status, BMI > 28, No (%): 11 (21)

Overall

- Sample size (randomized): 107
- Sample size (received intervention): 107
- Male gender, No (%): 17 (15.9%)
- Female gender, No (%): 90 (84.1%)
- Nutritional status, BMI 18-28, No (%): 74 (69.2%)
- Nutritional status, BMI > 28, No (%): 21 (19.6%)

Included criteria: patients with diagnosis of proximal fracture of the pelvis due to an accidential fall, age > 65 years, eligible for prosthetic surgery

Excluded criteria: neurologically or atherosclerotic-based dementia syndromes, unable to swallow or understand instructions, pathological fractures

Group differences: groups were comparable at baseline

Interventions	**Intervention characteristics** Intervention: mixed nutritional supplements (L-carnitine, L-leucine, calcium, magnesium, vitamin D) • Type of diet/supplementation: water soluble sachets • Macronutrients and micronutrients: 5 compounds supplement (Restorfast): L-carnitine (345 mg), calcium (500 mg), magnesium (250 mg), vitamin D (5 µg), L-leucine (500 mg) • Energy (kcal/kg/d): - • Amount of supplementation: 1 sachet/d • Mode of feeding: enteral • Intervention period (days): 42 Control group (standard nutrition) • Type of diet/supplementation: normal hospital diet • Macronutrients and micronutrients: no additinal micronutrients • Mode of feeding: enteral
Outcomes	PU incidence • Outcome type: dichotomous outcome • Reporting: fully reported • Direction: lower is better • Data value: endpoint Length of hospital stay (days) • Outcome type: continuous outcome • Direction: lower is better • Data value: endpoint

Derossi 2009 *(Continued)*

Identification	**Sponsorship source:** no information **Country:** Italy **Setting:** hospital **Authors:** Derossi, D., Bo, A., Bergonzi, R., Scivoletto G. **Institution:** Divisione di Ortopedia, Ospedale A. Uboldo **Email:** - **Address:** Via Uboldo 21, 20063 Cernusco sul Naviglio (Milano), Italy
Notes	

Desneves 2005

Study characteristics	
Methods	**Treatment study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group 1 • Sample size (randomized): 5 • Sample size (received intervention): - • Age, mean (SEM), years: 83.2 (1.1) • Male gender, No (%): 3 (60.0) • Female gender, No (%): 2 (40.0) • Dementia diagnosis, No (%): 0 • BMI, mean (SEM): 20.6 (1.5) • PU location: heel, No (%): 1 (20.0) • PU location: sacrum, No (%): 3 (60.0) • PU location: ischium, No (%): 1 (20.0) • PU stage 2, No (%): 3 (60.0) • PU stage 3, No (%): 1 (20.0) • PU stage 4, No (%): 1 (20.0) Intervention group 2 • Sample size (randomized): 5 • Sample size (received intervention): - • Age, mean (SEM), years: 75.6 (5.9) • Male gender, No (%): 3 (60.0) • Female gender, No (%): 2 (40.0) • Dementia diagnosis, No (%): 1 (20.0) • BMI, mean (SEM): 25.6 (0.8) • PU location: heel, No (%): 2 (40.0) • PU location: sacrum, No (%): 1 (20.0) • PU location: ischium, No (%): 1 (20.0)

Desneves 2005 *(Continued)*

- PU location: ankle, No (%): 1 (20.0)
- PU stage 2, No (%): 5 (100.0)

Control group

- Sample size (randomized): 6
- Sample size (received intervention): -
- Age, mean (SEM), years: 63.0 (9.9)
- Male gender, No (%): 4 (66.7)
- Female gender, No (%): 2 (33.3)
- Dementia diagnosis, No (%): 0
- BMI, mean (SEM): 24.4 (1.0)
- PU location: heel, No (%): 2 (33.3)
- PU location: sacrum, No (%): 1 (16.6)
- PU location: perineal, No (%): 1 (16.6)
- PU location: ankle, No (%): 1 (16.6)
- PU location: toe, No (%): 1 (16.6)
- PU stage 2, No (%): 4 (66.7)
- PU stage 3, No (%): 2 (33.3)

Overall

- Sample size (randomized): 16
- Sample size (received intervention): -
- Male gender, No (%): 10 (62.5)
- Female gender, No (%): 6 (37.5)
- Dementia diagnosis, No (%): 1 (6.3)
- PU location: heel, No (%): 5 (31.3)
- PU location: sacrum, No (%): 5 (31.3)
- PU location: ischium, No (%): 2 (12.5)
- PU location: perineal, No (%): 1 (6.3)
- PU location: ankle, No (%): 2 (12.5)
- PU location: toe, No (%): 1 (6.3)
- PU stage 2, No (%): 12 (75.0)
- PU stage 3, No (%): 3 (18.8)
- PU stage 4, No (%): 1 (6.3)

Included criteria: inpatients from Austin Health (Melbourne, Australia) with either a stage 2, 3 or 4 PU were recruited for the study in order of admission to the wards. Patients were selected from aged care or spinal injury wards as these wards were previously found to possess a high prevalence of PUs.

Excluded criteria: individuals with a clinical suspicion or diagnosis of osteomyelitis were excluded as osteomyelitis can cause skin ulcers that have a different aetiology to PUs. Also excluded were patients with diabetes mellitus, individuals receiving enteral or parenteral nutrition support or individuals prescribed hydroxyurea or greater than 10 mg of steroids/day as these factors all inhibit wound healing.

Group differences: patients randomised to diet intervention group 1 had a significantly lower BMI compared to patients allocated to intervention group 2 and control group. Mean age was lower in intervention group 1 compared to group 2 and contol group.

Interventions	**Intervention characteristics** Intervention 1: mixed nutritional supplements: (protein, arginine, zinc and antioxidants) • Type of diet/supplementation: arginine-containing ONS

Desneves 2005 *(Continued)*

	• Macronutrients and micronutrients: 21 g protein, 0 g fat, 500 mg vitamin C, 30 mg zinc, 9 g arginine • Energy: additional 2100 kJ (500 kcal) • Amount of supplementation: 2 packets • Mode of feeding: enteral • Intervention period (days): 21 Intervention 2: protein supplement • Type of diet/supplementation: ONS • Macronutrients and micronutrients: 18 g protein, 0 g fat, 72 mg vitamin C, 7.5 mg zinc • Energy: additional 2100 kJ (500 kcal) • Amount of supplementation: 2 packets • Mode of feeding: enteral • Intervention period (days): 21 Control (standard hospital diet) • Type of diets/supplementation: standard hospital diet, no supplement • Macronutrients and micronutrients: no addition • Energy (kcal): no addition • Mode of feeding: enteral • Intervention period (days): 21
Outcomes	PUSH score • Outcome type: continuous outcome • Direction: lower is better • Data value: change from baseline Death during the study period • Outcome type: adverse event • Direction: lower is better • Data value: endpoint
Identification	**Sponsorship source:** Windermere Foundation Ltd. **Country:** Australia **Setting:** inpatient care (aged care or spinal injury) **Authors:** Desneves, K.J., Todorovic, B.E., Cassara, A., Crowe, T.C. **Institution:** Department of Nutrition and Dietetics, Austin Health **Email:** tim.crowe@deakin.edu.au **Address:** T.C. Crowe, School of Exercise and Nutrition Sciences, Deakin University, Burwood Hwy, Burwood 3125, Australia
Notes	

Ek 1991

Study characteristics	
Methods	**Prevention and treatment study**

Ek 1991 *(Continued)*

	Study design: RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • No information on baseline characteristics Control group • No information on baseline characteristics Overall • Sample size (randomized): 501 • Sample size (received intervention): 451 • Age, mean (SD), years: 80.1 (8.5) • Male gender, No (%): 190 (37.9) • Female gender, No (%): 311 (62.1) • Dementia diagnosis, No (%): 77 (15.6) • Nutritional status (malnutrition), No (%): 125 (28.5) • Pre-existing PU, No (%): 70 (14.1) **Included criteria:** remaining at hospital for > 3 weeks **Excluded criteria:** no information **Group differences:** no information
Interventions	**Intervention characteristics** Intervention: mixed nutritional supplements (high energy, high protein and micronutrients) • Type of diets/supplementation: standard hospital diet + oral nutritional supplement • Macronutrients and micronutrients: each 100 mL contained 4 g protein, 4 g fat, 11.8 g carbohydrates, 419 kJ and minerals and vitamins • Energy: 2.200 kcal + 400 additional kcal/d • Amount of supplementation: 2 times/d 200 mL (all in all 400 mL) • Mode of feeding: enteral • Intervention period: up to 26 weeks Control group: standard diet • Type of diet/supplementation: standard hospital diet • Macronutrients and micronutrients: no addition • Energy: 2,200 kcal/d • Mode of feeding: enteral
Outcomes	New PUs • Outcome type: dichotomous outcome • Direction: lower is better Complete healing • Outcome type: dichotomous outcome • Direction: higher is better PU improvement

Ek 1991 *(Continued)*

- Outcome type: dichotomous outcome
- Direction: higher is better

Identification	**Sponsorship source:** grants from the Swedish Medical Research Council and the Research Fund of the County of Ostergotland. **Country:** Sweden **Setting:** Long-term care clinic of an Universival Hospital **Authors:** Ek, A.C., Unosson, M, Larsson, J., von Schenk, H., Bjurulf, P. **Institution:** Departments of Caring Sciences, Surgery, Clinical Chemistry and Preventive and Social Medicine,University Hospital **Email:** - **Address:** University Hospital, S-581 85, Linkiiping, Sweden
Notes	

Hartgrink 1998

Study characteristics	
Methods	**Prevention study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 70 • Sample size (received intervention): 62 • Age, mean (SD), years: 84.0 (7.1) • Male gender, No (%): 10 (16.1) • Female gender, No (%): 52 (83.9) • Pressure-sore risk score, mean (SD): 9.0 (1.3) • Pre-existing PU: stage 1, No (%): 10 (16.1) Control group • Sample size (randomized): 70 • Sample size (received intervention): 67 • Age, mean (SD), years: 83.3 (8.1) • Male gender, No (%): 6 (9.0) • Female gender, No (%): 61 (91.0) • Pressure-sore risk score, mean (SD): 9.2 (1.3) • Pre-existing PU: stage 1, No (%): 10 (14.9) Overall • Sample size (randomized): 140 • Sample size (received intervention): 129 • Male gender, No (%): 16 (12.4)

Hartgrink 1998 *(Continued)*

- Female gender, No (%): 113 (87.6)
- Pre-existing PU: stage 1, No (%): 20 (15.5)

Included criteria: fracture of the hip, pressure-sore risk score of ≥ 8 points (following Bakker 1985)

Excluded criteria: existing pressure sores of ≥ stage 2 at admission

Group differences: experimental group had more male participants

Interventions	**Intervention characteristics** Intervention: protein supplement • Type of diet/supplementation: standard hospital diet plus supplement (Nutrison Steriflo Energy-plus) via nasogastric tube • Macronutrients and micronutrients: additional 60 g protein • Energy: plus 1500 kcal/d • Amount of supplementation: 1000 mL • Mode of feeding: enteral with nasogastric tube (in the night) • Intervention period: 14 days Control group: standard diet • Type of diet/supplementation: standard hospital diet • Macronutrients and micronutrients: not reported • Energy: not reported • Mode of feeding: enteral • Intervention period: 14 days
Outcomes	Incidence of clinically relevant PUs (≥ stage 2) • Outcome type: dichotomous outcome • Direction: lower is better • Data value: endpoint Death during study period (2 weeks) • Outcome type: adverse event • Reporting: fully reported • Direction: lower is better • Data value: endpoint
Identification	**Sponsorship source:** Nutricia corp., Netherlands sponsored the tube feeding and the nasogastric tubes **Country:** Netherlands **Setting:** Hospital, Department of Surgery **Authors:** Hartgrink, H.H., Wille, J., König, P., Hermans, J., Breslau, J.P. **Institution:** Departments of Surgery, Red Cross Hospital, The Hague and Leiden University Medical Center **Email:** - **Address:** H. H. Hartgrink, M.D.,Leiden University Medical Center, Department of Surgery, K6 50, PO Box 9600, 2300 RC Leiden, The Netherlands
Notes	25/62 participants accepted nasogastric tube for > 1 week, 16 participants for 2 weeks.

Houwing 2003

Study characteristics	
Methods	**Prevention study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 51 • Sample size (received intervention): 51 • Age, mean (SD), years: 81.5 (0.9) • Male gender, No (%): 11 (21.6) • Female gender, No (%): 40 (78.4) • BMI, mean (SD): 24.2 (0.5) • PU risk score (CBO-risk-assessment), mean (SD): 11.1 (0.3) Control group • Sample size (randomized): 52 • Sample size (received intervention): 52 • Age, mean (SD), years: 80.5 (1.3) • Male gender, No (%): 8 (15.4) • Female gender, No (%): 44 (84.6) • BMI, mean (SD): 23.7 (0.5) • PU risk score (CBO-risk-assessment), mean (SD): 11.2 (0.2) Overall • Sample size (randomized): 103 • Sample size (received intervention): 103 • Male gender, No (%): 19 (18.4) • Female gender, No (%): 84 (81.6) **Included criteria:** patients with a hip fracture **Excluded criteria:** terminal care, metastatic hip fracture, insulin-dependent diabetes, renal disease (creatinine > 176 mmol/L), hepatic disease, morbid obesity (BMI > 40), need for therapeutic diet incompatible with supplementation and pregnancy or lactation **Group differences:** no significant group differences
Interventions	**Intervention characteristics** Intervention: mixed nutritional supplements: protein, arginine, zinc and antioxidants • Type of diet/supplementation: oral formula (Cubitan) enriched in arginine, zinc and antioxidant oligo elements • Macronutrients and micronutrients: arginine, zinc and antioxidant oligoelements (for 100 mL: 10 g protein, arginine 1.5 g, zinc 4.5 mg, copper 675 mcg, manganese 1.3 mg, vitamin E (a-tocopherol) 19.0 mg) • Energy: 503.2 kcal (29.8% from protein, 45.2% from carbohydrates, 25.0% from fat) • Amount of supplementation: 2 bottles, 400 mL in total • Mode of feeding: enteral

Houwing 2003 *(Continued)*

	• Intervention period: 28 days or until discharge Control: placebo • Type of diet/supplementation: non-caloric, water-based drink containing only sweeteners, colourants and flavourings • Macronutrients and micronutrients: no additional • Energy: no additional • Amount of supplementation: 2 bottles, 400 mL in total • Mode of feeding: enteral • Intervention period: 28 days or until discharge
Outcomes	Incidence of PU • Outcome type: dichotomous outcome • Reporting: fully reported • Direction: lower is better • Data value: endpoint Incidence stage 1 PU • Outcome type: dichotomous outcome • Reporting: fully reported • Direction: lower is better • Data value: endpoint Incidence stage 2 PU • Outcome type: dichotomous outcome • Direction: lower is better • Data value: endpoint Maximal PU size • Outcome type: continuous outcome • Direction: lower is better • Data value: endpoint
Identification	**Sponsorship source:** funded by Numico Research BV, Wageningen, the Netherlands **Country:** The Netherlands **Setting:** hospital, 3 centres treating people with hip fractures **Authors:** Houwing, R. H.; Rozendaal, M.; Wouters-Wesseling, W.; Beulens, J. W.; Buskens, E.; Haalboom, J. R **Institution:** Deventer Ziekenhuis, Department of Dermatology **Email:** - **Address:** H.J.P. Fesevurstraat 7, 7415 CM, Postbus 5001, 7400GC Deventer, The Netherlands
Notes	

Lee 2006

Study characteristics

Lee 2006 *(Continued)*

Methods	**Treatment study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 56 • Sample size (received intervention): 44 • BMI, mean (SD): 27 (8.8) • PUSH score week 0, mean (SD): 9.11 (4.15) Control group • Sample size (randomized): 33 • Sample size (received intervention): 27 • BMI, mean (SD): 27 (7.9) • PUSH score week 0, mean (SD): 6.07 (2.65) Overall • Sample size (randomized): 89 • Sample size (received intervention): 71 **Included criteria:** resident of long-term-care facility with PU (at least stage 2) **Excluded criteria:** terminal diagnosis, hospice care, protein-restricted diet due to renal insufficiency, active metabolic or gastrointestinal diseases that might interfere with nutrient absorption, distribution, metabolism, or excretion, food allergies, or use of corticosteroids or antibiotics for wound infection. **Group differences:** no information on baseline PUs in intervention and control group, differences in PUSH score at week 0 between groups (mean 9.11 versus 6.08)
Interventions	**Intervention characteristics** Intervention group: collagen supplement • Type of diet/supplementation: fortified collagen protein hydrolysate ONS • Macronutrients and micronutrients: 15 g protein in a 45 mL unit dose • Amount of supplementation: as identified by the label on the individual dose for nutritional supplementation • Mode of feeding: enteral • Intervention period: 56 days Control group (placebo) • Type of diet/supplementation: non-caloric placebo product insdistinguishable from study product in terms of colour, taste and texture • Macronutrients and micronutrients: none • Amount of supplementation: - • Mode of feeding: enteral • Intervention period: 56 days
Outcomes	PU healing: PUSH score • Outcome type: continuous outcome

Lee 2006 *(Continued)*

- Reporting: fully reported
- Direction: lower is better
- Data value: change from baseline

Death during the study period

- Outcome type: dichotomous outcome
- Direction: lower is better
- Data value: endpoint

Identification	**Sponsorship source:** Medical Nutrition USA, Inc. Englewood **Country:** USA **Setting:** 23 long-term-care facilities **Authors:** Lee, S. K.; Posthauer, M. E.; Dorner, B.; Redovian, V.; Maloney, M. J. **Institution:** Northeast Surgical Association of Ohio **Email:** - **Address:** -
Notes	No further information on the composition of the supplement

Leigh 2012

Study characteristics	
Methods	**Treatment study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group 1 • Sample size (randomized): 15 • Sample size (received intervention): 11 • Age, mean (SEM), years: 67.5 (4.9) • Male gender, No (%): 6 (54.6) • Female gender, No (%): 5 (45.4) • Albumin (g/L): 28.8 (1.4) • BMI, mean (SEM): 26.7 (2.0) • PU stage 2, No: 10 • PU stage 3, No: 3 • PU stage 4, No: 1 • PU location sacrum, No: 6 • PU location heel, No: 3 • PU location ischium, No: 2 • PU location ankle/elbow, No: 2 • PU location trochanter, No: 1 • PUSH score, mean (SEM): 8.1 (1.0) • Number of PUs, No: 14

Leigh 2012 *(Continued)*

Intervention group 2

- Sample size (randomized): 14
- Sample size (received intervention): 12
- Age, mean (SEM), years: 69.8 (5.2)
- Male gender, No (%): 8 (66.7)
- Female gender, No (%): 4 (33.3)
- Albumin (g/L): 28.3 (1.5)
- BMI, mean (SEM): 26.9 (2.5
- PU stage 2 No: 13
- PU stage 3, No: 3
- PU stage 4, No: 1
- PU location sacrum, No: 4
- PU location heel, No: 6
- PU location ischium, No: 5
- PU location knee, No: 2
- PUSH score, mean (SEM): 8.9 (0.7)
- Number of PUs, No: 17

Overall

- Sample size (randomized): 29
- Sample size (received intervention): 23
- Male gender, No (%): 14 (60.1)
- Female gender, No (%): 9 (39.9)

Included criteria: Inpatients were eligible for inclusion if they had a stage 2, 3 or 4 PU not showing signs of healing, were consuming an oral diet and had not yet started taking an arginine-containing supplement. A non-healing PU was determined by reviewing nursing and medical notes; if the PU measurements/descriptions had not improved over the previous 2 weeks, the PU was considered as not showing signs of healing.

Excluded criteria: patients with evidence of sepsis, an acute gastrointestinal surgery, those receiving dialysis, individuals receiving hydroxyurea or > 10 mg of prednisolone or 1.5 mg dexamethasone/d, individuals with a clinical suspicion of osteomyelitis

Group differences: no significant differences in participants' age, gender, BMI, PU stage and PUSH scores, difference in consumption of energy (P = 0.036) and protein (P = 0.018) between the groups, with the 9.0 g arginine group consuming higher amounts

Interventions	**Intervention characteristics** Intervention group 1: mixed nutritional supplements 9 g: arginine, vitamin C and vitamin E • Type of diet/supplementation: standard hospital diet plus 9 g mixed micronutrient powder • Macronutrients and micronutrients: 9 g arginine (2 sachets of Arginaid, Nestle Medical Nutrition), each sachet (in the form of a powder) weighed 9.2 g and contained 4.5 g arginine, 4 g carbohydrate, 155 mg vitamin C and 40.5 mg vitamin E • Amount of supplementation: 2 sachets mixed with 200 mL of water • Mode of feeding: enteral. The arginine powder in the sachet was mixed thoroughly with 200 mL of water before swallowing, as per the manufacturer's directions. • Intervention period: 3 weeks Intervention group 2: mixed nutritional supplements 4.5 g: arginine, vitamin C and vitamin E • Type of diet/supplementation: standard hospital diet plus 4.5 g mixed micronutrient powder

Leigh 2012 *(Continued)*

	• Macronutrients and micronutrients: 4.5 g arginine (1 sachet of Arginaid, Nestle Medical Nutrition), each sachet (in the form of a powder) weighed 9.2 g and contained 4.5 g arginine, 4 g carbohydrate, 155 mg vitamin C and 40.5 mg vitamin E • Amount of supplementation: 1 sachet mixed with 200 mL of water • Mode of feeding: enteral. The arginine powder in the sachet was mixed thoroughly with 200 mL of water before swallowing, as per the manufacturer's directions. • Intervention period: 3 weeks
Outcomes	PUSH data extrapolated from figure • Outcome type: continuous • Outcome direction: lower is better • Data value: change from baseline Full healing time, weeks (estimated time) • Outcome type: continuous outcome Acceptance /agreement to take the supplement • Outcome type: dichotomous • Outcome data value: endpoint Adverse effects (not specified) • Outcome type: dichotomous • Outcome data value: endpoint
Identification	**Sponsorship source:** no external funding source **Country:** Australia **Setting:** hospital (acute inpatient and rehabilitation services) **Authors:** Leigh, B.; Desneves, K.; Rafferty, J.; Pearce, L.; King, S.; Woodward, M. C.; Brown, D.; Martin, R.; Crowe, T. C. **Institution:** Austin Health (Melbourne, Australia) **Email:** tim.crowe@deakin.edu.au **Address:** Burwood, Australia
Notes	This study was in the previous version of the review as 'awaiting assessment'.

Meaume 2009

Study characteristics	
Methods	**Treatment study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 89

Meaume 2009 *(Continued)*

- Sample size (received intervention): 85
- Age, mean (SD), years: 81.0 (8.2)
- Male gender, No (%): 29 (34.1)
- Female gender, No (%): 56 (65.9)
- BMI, mean (SD): 27.1 (6.5)
- Malnutrition screening score (MNA), mean (SD): 17.6 (3.2)
- Braden Scale Score, mean (SD): 17.6 (3.2)
- PU stage 2, No (%): 33 (38.8)
- PU stage 2 or 3, No (%): 40 (47.1)
- PU stage 3, No (%): 12 (14.1)

Control group

- Sample size (randomized): 76
- Sample size (received intervention): 75
- Age, mean (SD), years: 80.5 (9.6)
- Male gender, No (%): 39 (52.6)
- Female gender, No (%): 36 (47.4)
- BMI, mean (SD): 26.7 (5.9)
- Malnutrition screening score (MNA), mean (SD): 17.6 (4.6)
- Braden Scale Score, mean (SD): 18.0 (3.2)
- PU stage 2, No (%): 24 (32.0)
- PU stage 2 or 3, No (%): 40 (53.3)
- PU stage 3, No (%): 11 (14.7)

Overall

- Sample size (randomized): 165
- Sample size (received intervention): 160
- Age, mean (SD), years: 80.8 (8.8)
- Male gender, No (%): 68 (42.5)
- Female gender, No (%): 92 (57.5)
- BMI, mean (SD): 26.9 (6.2)
- Braden Scale Score, mean (SD): 17.8 (3.2)
- PU stage 2, No (%): 57 (26.3)
- PU stage 2 or 3, No (%): 80 (50.0)
- PU stage 3, No (%): 23 (14.4)

Included criteria: men or women over the age of 60 years who have given their written informed consent to participate in the study; heel PU (NPUAP Stage 2 or 3) occurring after accidental immobilization; ulcer in the process of recovery with early signs of granulation tissue (at least 10% of red tissue on colour scale)

Excluded criteria: patients confined to bed 24 h/d before the episode triggering development of the PU; PU entirely covered by necrosis or fibrin, infected ulcer; poorly controlled type 1 or 2 diabetes, dialysed patient, active neoplastic disease; parenteral nutrition, serum albumin < 22 g/L; advanced peripheral arterial occlusive disease (ABPI (ankle brachial pressure index) ranging between 0.80 and 1.3 withpresence of distal pulses)

Group differences: imbalance in sex ratio. Intervention group had a higher proportion of women, but this does not affect the study results. Ulcer area was unbalanced between groups with a significant higher proportion of small ulcers in placebo group

Interventions	**Intervention characteristics** Intervention: amino acid supplement: (ornithine alpha-ketoglutarate)

Meaume 2009 *(Continued)*

	• Type of diet/supplementation: ONS, mixed in 200 mL of water or mixed with food • Macronutrients and micronutrients: an amino acid salt composed of 2 molecules of ornithine for 1 molecule of alpha-ketoglutarate; a protein intake of 1.2-1.5 g/kg/day was recommended. • Amount of supplementation: 1 sachet (10 g) a day • Mode of feeding: enteral • Intervention period: 42 days Control: placebo • Type of diet/supplementation: 1 sachet of placebo (similar aspect and taste) • Macronutrients and micronutrients: a protein intake of 1.2-1.5 g/kg/d was recommended. • Amount of supplementation: 1 sachet/d • Mode of feeding: enteral • Intervention period: 42 days
Outcomes	PU area change (cm^2): population with baseline PU area ≤ 8 cm^2 • Outcome type: continuous outcome • Direction: higher is better • Data value: change from baseline PU area change (%): population with baseline PU area ≤ 8 cm^2 • Outcome type: continuous outcome > 90% reduction in PU area at 6 weeks (population with baseline PU area ≤ 8 cm^2) • Outcome type: dichotomous outcome • Direction: higher is better Closure rate in population with baseline PU area ≤ 8 cm^2 • Outcome type: continuous outcome • Direction: higher is better Adverse events (deaths) • Outcome type: dichotomous outcome • Direction: lower is better • Data value: endpoint Other serious adverse events • Outcome type: dichotomous outcome • Direction: lower is better • Data value: endpoint At least 1 adverse effect • Outcome type: dichotomous outcome • Direction: lower is better • Data value: change from baseline
Identification	**Sponsorship source:** sponsored by a grant from CHIESI France and Italy. **Country:** Bulgaria, France, Germany, Italy, Romania, Spain **Setting:** hospitals (67 wards: geriatric, internal medicine, physical medicine and rehabilitation, trauma, plastic surgery, cardiology, neurology and dermatology), in- and outpatient settings

Meaume 2009 *(Continued)*

	Authors: Meaume, S., Kerihuel, J.C., Constans, T., Teot, L., Lerebours, E., Kern, J., Bordel Marchasson, I. **Institution**: Department of Gerontology, Charles Foix Hospital, Ivry-sur-Seine, Paris **Email:** - **Address:** Meaume S., Head of Department, Department of Gerontology, Charles Foix Hospital, Ivry-sur-Seine, Paris
Notes	

Miu 2021

Study characteristics	
Methods	**Treatment study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 47 • Sample size (received intervention): 47 • Age, mean (SD): 83.04 (11.46) • Male gender, No (%): 18 (38.3) • Female gender, No (%): 29 (61.7) • BMI, mean (SD): 18.57 (6.38) • Charlson Comorbidity Index (CCI) (median): 2 • Tube feeding, n (%): - • Diabetes, (%): 14 (30.4) • PUSH score, mean (SD): 12.99 (3.6) • PU size (cm^2): 34.97 (26.7) Control group • Sample size (randomized): 40 • Sample size (received intervention): 40 • Age, mean (SD): 81.42 (13.03) • Male gender, No (%): 15 (37.5) • Female gender, No (%): 25 (62.5) • BMI, mean (SD): 17.76 (4.77) • Charlson Comorbidity Index (CCI) (median): 3 • Tube feeding, n (%): - • Diabetes, (%): 11 (27.5) • PUSH score, mean (SD): 14.64 (1.83) • PU size (cm^2): 38.15 (36.7) Overall • Sample size (randomized): 87 • Sample size (received intervention): 87

Miu 2021 *(Continued)*

- Age, mean (SD): 82.48 (12.15)
- Male gender, No (%): 33 (37.9)
- Female gender, No (%): 54 (62.1)
- BMI, mean (SD): 18.2 (5.68)
- Charlson Comorbidity Index (CCI) (median): 2.53 (1.56)
- Tube feeding, n (%): 41 (47.1)
- Diabetes, (%): 25 (28.7)

Included criteria: patients aged ≥ 18 years, with at least 1 stage 3–4 PU according to the revised EPUAP classification system

Excluded criteria: cellulitis, infected wounds, osteomyelitis or sepsis; patients requiring dietary restriction; patients with poorly controlled diabetes mellitus as defined by an Hba1c > 8.5% and patients receiving palliative care

Group differences: significant baseline difference in PUSH score means: control group more severe PUSH score (14.64 vs 12.99), groups differ with regard to PU size: intervention: 34.97 cm^2 (SD26.7) versus control 38.15 cm^2 (SD 36.7)

Interventions	**Intervention characteristics** Intervention: amino acid supplement (arginine, glutamine and β-hydroxy-β-methylbutyrate (HMB)) • Type of diet/suppmelentation: sackets of nutritional supplement • Macronutrients and micronutrients: at least 1.2 g/kg/d of protein, additional 2 sachets of a mixture of arginine, glutamine and HMB (Abound) • Energy: at least 30 kcal/kg/d • Amount of supplementation: additonal 200 mL daily • Mode of feeding: enteral • Intervention period: 4 weeks Control: standard diet • Type of diet/suppmelentation: standard nutritional care • Macronutrients and micronutrients: at least 1.2 g/kg/d of protein • Energy (kcal/kg/d): at least 30 kcal/kg/d • Amount of supplementation: - • Mode of feeding: enteral • Intervention period: 4 weeks
Outcomes	PU size (cm^2), weeks 2 and 4 extrapolated from figure • Outcome type: continuous outcome • Direction: lower is better • Data value: endpoint Progress of PU healing (PUSH score): weeks 2 and 4 extrapolated from figure • Outcome type: continuous outcome • Direction: lower is better • Data value: change from baseline Body weight • Outcome type: continuous outcome • Scale: kg • Direction: higher is better • Data value: change from baseline

Miu 2021 *(Continued)*

	Length of hospitalization (days) • Outcome type: continuous outcome • Data value: endpoint Inpatient mortality • Outcome type: adverse event • Direction: lower is better • Data value: endpoint 6-month mortality • Outcome type: adverse event • Reporting: fully reported • Direction: lower is better • Data value: endpoint Death during study period (4 weeks) • Outcome type: adverse event • Direction: lower is better Treatment-related adverse event • Outcome type: adverse event • Direction: lower is better PU healing rate/d (first 2 weesk) • Outcome type: continuous outcome • Reporting: fully reported • Direction: higher is better • Data value: change from baseline PU healing rate/d • Outcome type: continuous outcome • Reporting: fully reported • Direction: higher is better • Data value: change from baseline
Identification	**Sponsorship source:** no information **Country:** China **Setting:** chospital **Authors:** Miu KYD , Lo KM , Lam KYE, Lam PS **Institution:** Department of Rehabilitation and Extended Care, Wong Tai Sin Hospital, Hong Kong **Email:** miuky@ha.org.hk **Address:** Department of Rehabilitationand Extended CareWong Tai Sin Hospital,Hong Kong
Notes	

Norris 1971

Study characteristics	
Methods	**Treatment study** **Study design:** RCT **Study grouping:** cross-over
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 10 Control group (placebo) • Sample size (randomized): 8 Overall • Sample size (randomized): 14 • Age, mean (SD), years: 59.3 (19.0) • Male gender, No (%): 9 (64.3) • Female gender, No (%): 5 (35.7) **Included criteria:** patients with PUs **Excluded criteria:** neoplastic disease, terminal phase of illness, superficial PUs, PUs where deep sinus tracts were involved **Group differences:** cross-over study with residents being own controls
Interventions	**Intervention characteristics** Intervention group: zinc sulphate • Type of diets/supplementation: capsule zinc sulphate • Macronutrients and micronutrients: 200 mg zinc sulphate • Amount of supplementation: 1 capsule • Mode of feeding: enteral • Intervention period: 84 days Control group: placebo • Type of diets/supplementation: placebo capsule • Macronutrients and micronutrients: placebo • Amount of supplementation: 1 capsule • Mode of feeding: enteral • Intervention period: 84 days
Outcomes	Change of PUs volume (mL) • Outcome type: continuous outcome • Direction: higher is better Death in study period • Outcome type: dichotomous outcome • Reporting: fully reported • Direction: lower is better

Norris 1971 *(Continued)*

	• Data value: endpoint
Identification	**Sponsorship source:** C.R. Canfield and Company (supplied the zinc sulfate and defrayed incidental costs) **Country:** USA **Setting:** hospital **Authors:** Norris, J.R., Reynolds R.E. **Institution:** Baltimore City Hospitals **Email:** - **Address:** J.R. Norris, Department of Chronic MEdical Care, Baltimore City Hospitals, York Road Medical Group, 2045 York Road, Timonium, Maryland 21093
Notes	

Ohura 2011

Study characteristics	
Methods	**Treatment study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 30 • Sample size (received intervention): 21 • Age, mean (SD), years: 81.4 (8.13) • Male gender, No (%): 6 (28.6) • Female gender, No (%): 15 (71.4) • BMI, mean (SD): 18.6 (4.04) • Braden Scale Score, median: 11 Control group • Sample size (randomized): 30 • Sample size (received intervention): 29 • Age, mean (SD), years: 80.6 (8.91) • Male gender, No (%): 10 (34.5) • Female gender, No (%): 19 (65.5) • BMI, mean (SD): 17.11 (2.56) • Braden Scale Score, median: 11 Overall • Sample size (randomized): 60 • Sample size (received intervention): 50 • Male gender, No (%): 16 (32.0) • Female gender, No (%): 34 (68.0)

Ohura 2011 *(Continued)*

	• Dementia diagnosis, No (%): 18 (36.0) **Included criteria:** inpatients without dehydration with > 12 weeks of objective energy intake by tube feeding. Pressure ulcer at sacral, coccygeal, trochanteric, or calcaneal region. Stage must be 3 or 4 (NPUAP). Area of necrosis tissues < 20% of area of pressure ulcer, depth of pocket of pressure ulcer < 2 cm. Albumin 2.5-3.5 g/dL; OH scale: < 8.5; Braden scale: 9-17 **Excluded criteria:** current condition or history of serious liver or renal disorder, severe diabetes mellitus, arteriosclerosis obliterans, or a malignant tumour (within the past 5 years). Patients with unmanageable severe general conditon or unevaluable pressure ulcer wounds (existence of necrotic tissue in ≥ 20% of the wound surface, wound before sharp debridement, ≥ 2 cm in depth of the undermining, multiple pressure ulcers and wound infection) were also excluded. **Group differences:** non evident
Interventions	**Intervention characteristics** Intervention: mixed nutritional supplements: high energy, high protein and micronutrients • Type of diet/supplementation:feeding via tube with defined formula and administred calories • Macronutrients and micronutrients: feeding formula (Racol) per 100 kcal: protein 4.38 g, fat 2.23 g, and carbohydrate 15.62 g, copper 125 mg and zinc 0.64 mg per 100 mL of product. The ratio of ω-3 to ω -6 essential fatty acids was 1:3 • Energy: according to the range of Basal Energy Expenditure (BEE, calculated from the Harris–Benedict equation) x active factor 1.1, x stress factor 1.3–1.5 • Amount of supplementation: offer an individual determined energy intake • Mode of feeding: enteral (tube feeding) • Intervention period: 84 days Control: standard diet • Type of diet/supplementation:feeding via tube with defined formula as before participating in the trial • Macronutrients and micronutrients: feeding formula (Racol) per 100 kcal: protein 4.38 g, fat 2.23 g, and carbohydrate 15.62 g, copper 125 mg and zinc 0.64 mg per 100 mL of product. The ratio of ω-3 to ω -6 essential fatty acids was 1:3 • Energy: same amount of calories as before participating in the trial • Amount of supplementation: standard care • Mode of feeding: enteral (tube feeding) • Intervention period: 84 days
Outcomes	Number of peopled healed • Outcome type: dichotomous outcome • Direction: higher is better Adverse effects (not specified) • Outcome type: dichotomous outcome • Direction: lower is better • Data value: endpoint
Identification	**Sponsorship source:** Health and Labor Sciences Research Grants **Country:** Japan **Setting:** hospitals (multicentre, the number of facilities was not specified) **Authors:** Ohura, T., Nakajo, T., Okada, S., Omura, K., Adachi, K. **Institution:** Pressure Ulcers and Wound Healing Research Center (Kojin-Kai)

Ohura 2011 *(Continued)*

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Address: Takehiko Ohura, Pressure Ulcers and Wound Healing Research Center (Kojin-Kai), 7F, H&B Plaza Bld. 1-1, South 3, West 2,Chuo-ku, Sapporo 060-0063, Japan.

Notes	

Pouyssegur 2015

Study characteristics	
Methods	**Treatment study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 108 • Sample size (received intervention): 88 • Age, mean (SD), years: 85.4 (7.1) • Male gender, No (%): 21 (23.9) • Female gender, No (%): 67 (76.1) • MMSE mean (SD): 18.1 (8.4) • Nutritional status (weight loss > 10% in 6 months), No (%): 21 (23.9) • BMI, mean (SD): 19.2 (2.9) • Malnutrition screening scores (MNA), mean, (SD): 14.5 (3.9) Control group • Sample size (randomized): 108 • Sample size (received intervention): 83 • Age, mean (SD), years: 86.8 (7.1) • Male gender, No (%): 14 (16.1) • Female gender, No (%): 69 (83.9) • MMSE mean (SD): 18.1 (8.3) • Nutritional status (weight loss > 10% in 6 months), No (%): 26 (29.9) • BMI, mean (SD): 19.2 (2.9) • Malnutrition screening scores (MNA mean), (SD): 14.7 (5.0) Overall • Sample size (randomized): 216 • Sample size (received intervention): 171 • Male gender, No (%): 35 (20.5) • Female gender, No (%): 136 (79.5) **Included criteria:** age > 70 years, malnutrition (based on the criteria weight loss survey, BMI and MNA); prescription of home-made sweets enriched with milk proteins and/or liquid or creamy ONSs was not an exclusion criteria. **Excluded criteria:** difficulty swallowing

Pouyssegur 2015 *(Continued)*

	Group differences: more residents with PUs in intervention group (18 out of 88 versus 8 out of 87). BMI, age, gender distribution are comparable
Interventions	**Intervention characteristics** Intervention: protein supplement • Type of diet/supplementation: cookies • Macronutrients and micronutrients: usual food regimen of the institution and 8 cookies a day with each cookie contained 1.44 g of protein (11.5 g of protein daily supplementation) • Energy: each cookie contained 30.5 kcal (244 kcal daily supplementation) • Amount of supplementation: 8 Protibis cookies daily (each weighted 6.5 g) • Mode of feeding: enteral • Intervention period: 6 weeks Control: standard diet • Type of diet/supplementation: standard hospital diet • Macronutrients and micronutrients: usual food regimen of the institution
Outcomes	Change in PU episodes • Outcome type: dichotomous outcome • Reporting: fully reported • Direction: lower is better • Data value: change from baseline Adverse effect: diarrhoea episodes • Outcome type: dichotomous outcome • Direction: lower is better • Data value: endpoint Adverse events (deaths) • Outcome type: dichotomous outcome • Reporting: fully reported • Direction: lower is better • Data value: endpoint Costs of care (EUR) based on the probability of events observed (bedsores, diarrhoea, falls, infection) and related mean costs • Outcome type: continuous outcome • Reporting: fully reported • Notes: (standard social protection)
Identification	**Sponsorship source:** supported by the French Ministry of Higher Education and Research (grant PTR200909037). There was no commercial sponsorship. **Country:** France **Setting:** nursing homes **Authors:** Pouyssegur, V.; Brocker, P.; Schneider, S. M.; Philip, J. L.; Barat, P.; Reichert, E.; Breugnon, F.; Brunet, D.; Civalleri, B.; Solere, J. P.; Bensussan, L.; Lupi-Pegurier, L. **Institution:** Laboratoire Micoralis EA7354, Faculté de Chirurgie Dentaire, Université Côte-d'Azur **Email:** valerie.pouyssegur-rougier@unice.fr

Pouyssegur 2015 *(Continued)*

	Address: Université Côte-d'Azur, 24, Avenue des Diables-Bleus, 06300 Nice, France.
Notes	Baseline sample size differs in figures and tables

Sugihara 2018

Study characteristics	
Methods	**Treatment study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group 1 • Sample size (randomized): 40 • Age, years, mean (SD): 38.0 (8.4) • Male, n (%): 25 (65.8) • Female, n (%): 13 (34.2) • Height, cm, mean (SD): 157 (8) • Weight, kg, mean (SD): 64.5 (6.9) • BMI, kg/m^2, mean (SD): 26.4 (3.4) • PUSH score, points, mean (SD): 12.00 (1.51) • PSST score, points, mean (SD): 29.71 (2.31) • PU area, cm^2, mean (SD): 12.16 (9.22) Intervention group 2 • Sample size (randomized): 40 • Age, years, mean (SD): 45.1 (12.1) • Male, n (%): 20 (57.1) • Female, n (%): 15 (42.9) • Height, cm, mean (SD): 153 (10) • Weight, kg, mean (SD): 60.6 (7.2) • BMI, kg/m^2, mean (SD): 25.8 (2.9) • PUSH score, points, mean (SD): 12.34 (1.92) • PSST score, points, mean (SD): 30.20 (1.69) • PU area, cm^2, mean (SD): 13.23 (9.56) Placebo • Sample size (randomized): 42 • Age, years, mean (SD): 46.4 (11.1) • Male, n (%): 17 (43.6) • Female, n (%): 22 (56.4) • Height, cm, mean (SD): 154 (9) • Weight, kg, mean (SD): 62.1 (6.8) • BMI, kg/m^2, mean (SD): 26.4 (3.3) • PUSH score, points, mean (SD): 11.92 (1.90) • PSST score, points, mean (SD): 29.79 (2.31) • PU area, cm^2, mean (SD): 12.85 (10.29)

Sugihara 2018 *(Continued)*

Overall

- Sample size (randomized): 122
- Age, years, mean (SD): 43.1 (10.5)
- Male, n (%): 62 (55.4)
- Female, n (%): 50 (44.6)
- Height, cm, mean (SD): 154.7 (9.0)
- Weight, kg, mean (SD): 62.4 (7.0)
- BMI, kg/m^2, mean (SD): 26.2 (3.2)
- PUSH score, points, mean (SD): 12.1 (1.8)
- PSST score, points, mean (SD): 29.9 (2.1)
- PU area, cm^2, mean (SD): 12.7 (9.7)

Included criteria: inpatients or outpatients of either sex who were aged between 18 and 70 years; had been diagnosed with stage 2 or 3 PUs, as defined by NPUAP; BMI 18.5-34.9 kg/m^2; exhibited a PU surface area of < 80 cm^2 (multiplication of the major and minor diameters of the PU surface); were suffering from a stage 2 or 3 PU (regardless of its location) with a PUSH (version 3.0) score of ≥ 5 that was likely to heal during the 6-month study period; and demonstrated moderate exudate production and a Braden score of ≥ 6.

Excluded criteria:

- Pregnant or lactating women
- Women of childbearing potential who were not taking adequate contraceptive measures
- Stage 4 PUs
- Being tube-fed
- Diabetic foot ulcers
- Immunotherapy or cytotoxic chemotherapy within the 60 days before enrollment
- Taken systemic steroids within the 30 days prior to enrollment
- Received topical therapy other than steroidal therapy during the 7 days prior to enrollment
- HIV-, hepatitis B virus-, or hepatitis C virus-positive
- Pre-existing demyelinating disorders
- Hepatic, renal, or metabolic disease that was likely to interfere with their participation in or completion of the study
- Arterial or venous disorders that had the potential to cause ulcerated wounds
- History of established diabetes mellitus and a fasting blood glucose level of > 200 mg/dL−1
- Any condition that would interfere with wound healing (e.g. a connective tissue disorder, immunological disorder, or clinical obesity)
- Malnourished
- Wounds caused by malignancy
- Burns or scalds
- Used any form of complementary alternative medicine in the preceding 2 months
- Known to exhibit hypersensitivity reactions to protein products
- Any dermatological condition or disorder that might interfere with the appropriate assessment or treatment of ulcers
- Current smokers
- Participated in any other clinical study during the 3 months prior to the study
- Unwilling or unable to comply with the study procedures
- Considered to be unsuitable candidates by the investigator for any reason

Group differences: intervention group 1 had more male participants and the participants were younger.

Additional PU treatment: participants were treated with antimicrobials, antiseptics, wound debridement, and wound dressing, as required.

Sugihara 2018 *(Continued)*

Interventions	**Intervention characteristics** Intervention 1: collagen - low dipeptide • Type of diet/supplementation: collagen hydrolysates supplementation, which had a low dipeptide content (< 0.01 g dipeptides per kg of product) • Macronutrients and micronutrients: 965 g/kg^{-1} protein, 0 g/kg^{-1} carbohydrates, 0 g/kg^{-1} fat, 2 g/kg^{-1} ash, 33 g/kg^{-1} moisture, mean molecular weights: 5.000 • Energy: 3860 kcal/kg^{-1} • Amount of supplementation: powder (5 g in aluminum sachet), dissolved in 250 mL water or milk • Mode of feeding: enteral (orally consume powder dissolved in water or milk in the morning and night after eating food) • Intervention period: 16 weeks Intervention 2: collagen - high dipeptide • Type of diet/supplementation: collagen hydrolysates supplementation which had a high dipeptide content (> 1 g dipeptides per kg of product) • Macronutrients and micronutrients: 894 g/kg^{-1} protein, 41 g/kg^{-1} carbohydrates, 0 g/kg^{-1} fat, 4 g/kg^{-1} ash, 61 g/kg^{-1} moisture, mean molecular weights: 1.200 • Energy: 3740 kcal/kg^{-1} • Amount of supplementation: powder (5 g in aluminum sachet), dissolved in 250 mL water or milk • Mode of feeding: enteral (orally consume powder dissolved in water or milk in the morning and night after eating food) • Intervention period: 16 weeks Control: placebo • Type of diet/supplementation: placebo, maltodextrin TK-16 • Macronutrients and micronutrients: 0 g/kg^{-1} protein, 960 g/kg^{-1} carbohydrates, 0 g/kg^{-1} fat, 0 g/kg^{-1} ash, 40 g/kg^{-1} moisture • Energy: 3840 kcal/kg^{-1} • Amount of supplementation: powder (5 g in aluminum sachet), dissolved in 250 mL water or milk • Mode of feeding: enteral (orally consume powder dissolved in water or milk in the morning and night after eating food) • Intervention period: 16 weeks
Outcomes	PUSH score • Outcome type: continuous outcome • Reporting: fully reported • Unit of measure: points • Direction: lower is better • Data value: endpoint PSST score • Outcome type: continuous outcome • Reporting: partially reported • Unit of measure: points • Direction: lower is better • Data value: endpoint PU area • Outcome type: continuous outcome • Reporting: partially reported

Sugihara 2018 *(Continued)*

- Unit of measure: cm^2
- Direction: lower is better
- Data value: endpoint

Reduction in the PUSH score of ≥ 5 points

- Outcome type: dichotomous outcome
- Reporting: fully reported
- Unit of measure: percentage and number of participants
- Direction: higher is better
- Data value: change from baseline

Reduction in the PSST score of ≥ 10 points

- Outcome type: dichotomous outcome
- Reporting: fully reported
- Unit of measure: percentage and number of participants
- Direction: higher is better
- Data value: change from baseline

Reduction in the PUSH score of 3–4 points

- Outcome type: dichotomous outcome
- Reporting: fully reported
- Unit of measure: percentage and number of participants
- Direction: higher is better
- Data value: change from baseline

Reduction in the PSST score of 5–9 points

- Outcome type: dichotomous outcome
- Reporting: fully reported
- Unit of measure: percentage and number of participants
- Direction: higher is better
- Data value: change from baseline

Reduction in the PUSH score of ≥ 3 points

- Outcome type: dichotomous outcome
- Reporting: fully reported
- Unit of measure: percentage and number of participants
- Direction: higher is better
- Data value: change from baseline

Reduction in the PSST score of ≥ 5 points

- Outcome type: dichotomous outcome
- Reporting: fully reported
- Unit of measure: percentage and number of participants
- Direction: higher is better
- Data value: change from baseline

Identification	**Sponsorship source:** Nitta Gelatin India ltd, Cochin, India Aurous Health Care Research and Development India Private Limited **Country:** India **Setting:** Hospital (inpatients)

Sugihara 2018 *(Continued)*

Authors: Sugihara, F, Inoue, N., Venkateswarathirukumara, S.

Institution: Nitta Gelatin; Aurous Health Care Research and Development Private Limited

Email: na-inoue@nitta-gelatin.co.jp

Address: Nitta Gelatin, Inc., 2-22 Futamata, Yao-city, Osaka, Japan

Notes

Taylor 1974

Study characteristics

Methods

Treatment study

Study design: RCT

Study grouping: parallel group

Participants

Baseline characteristics

Intervention group

- Sample size (randomized): 10

Control group

- Sample size (randomized): 10

Overall

- Sample size (randomized): 20
- Age years, mean (range): 74.5 (54-88)
- Male gender, n (%): 8 (40)
- Female gender, n (%): 12 (60)

Included criteria: surgical patients with PU

Excluded criteria: not stated

Group differences: none stated

Interventions

Intervention characteristics

Intervention: vitamin C

- Type of diet/supplementation: standard hospital diet plus vitamin C
- Macronutrients and micronutrients: ascorbic acid
- Amount of supplementation: 2 x 500 mg/d
- Mode of feeding: enteral
- Intervention period: up to 12 weeks

Control: placebo

- Type of diet/supplementation: standard hospital diet plus placebo
- Macronutrients and micronutrients: inert placebo
- Amount of supplementation: 2 pills/d
- Mode of feeding: enteral

Taylor 1974 *(Continued)*

	• Intervention period: up to 12 weeks
Outcomes	Complete healing • Outcome type: dichotomous outcome • Reporting: fully reported • Direction: higher is better • Data value: endpoint Mean reduction in PU area (%) • Outcome type: continuous outcome • Direction: higher is better • Data value: change from baseline PU healing • Outcome type: continuous outcome • Direction: higher is better
Identification	**Sponsorship source:** supplements provided by Merck Limited **Country:** UK **Setting:** Hospital, Department of Medicine (University Hospital) and Division of Surgery (Royal Infirmary) **Authors:** Taylor, T. V. **Institution:** University Hospital of South Manchester **Email:** - **Address:** I.W. Dymock, Department of Medicine, Withington Hospital, Manchester M20, 8L.R.
Notes	

Ter Riet 1995

Study characteristics	
Methods	**Treatment study** **Study design:** RCT (factorial design) **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 43 • Sample size (received intervention): 43 • Bad nutritional status (severely undernourished (clinical impression) or albumin ~30 g/L or upper arm fat area < 10th percentile (adjusted for sex and age) or upper arm muscle area < 10th percentile (adjusted for sex and age), %: 69.8 • BMI, median (25th and 75th percentile): 21.5 (17.0-24.3) • Bad wound status (muscle involvement and estimated time needed for closure of > 12 weeks or ulcer has been present for > 180 days), %: 34.9

Ter Riet 1995 *(Continued)*

- Overall bad PU status (stage 3 ulcer or any number of stage 4 ulcers or has suffered from PUs before), %: 65.1
- PU located on the trunk, %: 55.8
- PU stages 2 and 3, %: 86.0

Control group

- Sample size (randomized): 45
- Sample size (received intervention): 45
- Bad nutritional status (severely undernourished (clinical impression) or albumin ~30 g/L or upper arm fat area < 10th percentile (adjusted for sex and age) or upper arm muscle area < 10th percentile (adjusted for sex and age), %: 71.1
- BMI, median (25th and 75th percentile): 20.7 (18.5-24.1)
- Bad wound status (muscle involvement and estimated time needed for closure of > 12 weeks or ulcer has been present for > 180 days), %: 33.3
- Overall bad PU status (stage 3 ulcer or any number of stage 4 ulcers or has suffered from PUs before), %: 77.8
- PU located on the trunk, %: 62.2
- PU stages 2 and 3, %: 77.8

Overall

- Sample size (randomized): 88
- Sample size (received intervention): 88

Included criteria: patients having a PU (partial thickness skin loss or worse = stage 2 and higher); patiens with grade 2 only, if de-epithelialization had persisted for at least 7 days without interruption, patients with leg ulcers had to have a positive history of pressure on that site.

Excluded criteria: difficulties with swallowing or frequent vomiting, osteomyelitis in the ulcer area, idiopathic haemochromatosis, thalassemia major, sideroblastic anemia, Cushing's syndrome or disease, pregnancy, radiotherapy in the ulcer area, the use of antineoplastic agents or systemic glucocorticosteroids, a high probability to drop out within the 12-week follow-up period (terminally ill patients, patients for whom surgical treatment of the ulcer other than debridement had been planned), already taking vitamin C supplements in excess of 50 mg/d

Group differences: nutritional and PU status were similar between groups. The control group had a greater proportion of patients with very large ulcers.

Interventions	**Intervention characteristics**

Intervention: vitamin C

Experimental group (high vitamin C)

- Type of diet/supplementation: effervescent tablets with high vitamin C
- Macronutrients and micronutrients: 500 mg of vitamin C (Roche, Basel, Switzerland) 2 times/d
- Energy (kcal/kg/d): no addition
- Amount of supplementation: twice daily (in the morning and early evening)
- Mode of feeding: enteral
- Intervention period: 84 days

Control: placebo

- Type of diets/supplementation: effervescent tablets with low vitamin C
- Macronutrients and micronutrients: 10 mg of vitamin C 2 times/d
- Energy (kcal/kg/d): no addition
- Amount of supplementation: twice daily (in the morning and early evening)
- Mode of feeding: enteral

Ter Riet 1995 *(Continued)*

	• Intervention period: 84 days
Outcomes	PU surface reduction (cm^2/week) • Outcome type: continuous outcome • Reporting: fully reported • Direction: higher is better • Data value: change from baseline PU surface reduction (%) • Outcome type: continuous outcome • Direction: higher is better • Data value: change from baseline PU healing velocity (cm/week) • Outcome type: continuous outcome • Direction: higher is better • Data value: change from baseline PU volume reduction (mL/week) • Outcome type: continuous outcome • Direction: higher is better • Data value: change from baseline PU volume reduction (%/week) • Outcome type: continuous outcome • Reporting: partially reported • Direction: higher is better • Data value: change from baseline PU improvements in report mark/week • Outcome type: continuous outcome • Range: 1-10 • Direction: higher is better • Data value: change from baseline Mean clinical improvement (%/week) • Outcome type: continuous outcome • Range: −100% to +100% • Direction: higher is better • Data value: change from baseline Adverse events (deaths) • Outcome type: dichotomous outcome • Reporting: fully reported • Direction: lower is better • Data value: endpoint
Identification	**Sponsorship source:** supported by a grant of The Netherlands Organization for Scientific Research (NWO). Hoffmann-La Roche & Co., Ltd., Basel supplied the tablets and the plasma vitamin C determinations **Country:** The Netherlands

Ter Riet 1995 *(Continued)*

	Setting: Nursing homes (n = 11) and hospital (n = 1) **Authors:** Ter Riet, G. Kessels, A.G.H., Knipschid, P.G. **Institution:** Department of Epidemiology, University of Limburg **Email:** - **Address:** P.O. Box 616,620o MD Maastricht, The Netherlands
Notes	Factorial design with ultrasound as second intervention (high vitamin C plus ultrasound vs high vitamin C plus sham ultrasound vs low vitamin C plus ultrasound vs low vitamin C plus sham ultrasound). We only used data from sham ultrasound groups.

Theilla 2007

Study characteristics	
Methods	**Prevention and treatment study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 50 • Sample size (received intervention): 46 • Age, mean (SD), years: 57.0 (18.7) • Male gender, No (%): 29 (63.0) • Female gender, No (%): 17 (37.0) • BMI, mean (SD): 28.9 (6.2) Control group • Sample size (randomized): 50 • Sample size (received intervention): 49 • Age, mean (SD), years: 62.3 (17.2) • Male gender, No (%): 28 (57.1) • Female gender, No (%): 21 (42.9) • BMI, mean (SD): 26.5 (5.4) Overall • Sample size (randomized): 100 • Sample size (received intervention): 95 • Male gender, No (%): 57 (60.0) • Female gender, No (%): 38 (40.0) **Included criteria:** patients suffering from acute lung injury defined by a PaO2/FIO2 ratio < 250 **Excluded criteria:** head trauma, cerebral bleeding, coagulation disorders, those receiving steroids in a dose 40.25 mg/kg/day methylprednisolone or non-steroidal anti-inflammatory agents, < 18 years, and pregnant patients. Diarrhoea was noted and patients were excluded if loose stools occurred > 3 times.

Theilla 2007 *(Continued)*

	Group differences: patients' BMI at baseline was higher in the intervention group.
Interventions	**Intervention characteristics** Intervention: mixed nutritional supplements (antioxidants including ß-carotene, vitamin C and vitamin E) • Type of diet/supplementation: high-fat, low-carbohydrate enteral formula enriched with EPA, GLA and vitamins A, C and E • Macronutrient composition and micronutrients: 16.7% of energy in protein, 28.1% of energy in carbohydrates, 55.2% of energy in lipids, ß-carotene 5 mg/L, vitamin C 844 mg/L, vitamin E 317 IU/L • Amount of supplementation: start with 50 % of the REE x 1.25 to reach 1.25 x REE • Mode of feeding: enteral • Intervention period: 7 days Control: standard diet • Type of diet/supplementation: high-fat, low-carbohydrate standard enteral formula • Macronutrient composition and micronutrients: 16.7% of energy in protein, 28.1% of energy in carbohydrates, 55.2% of energy in lipids, ß-carotene no, vitamin C 317 mg/L, vitamin E 85 IU/L • Amount of supplementation: start with 50 % of the REE x 1.25 to reach 1.25 x REE • Mode of feeding: enteral • Intervention period: 7 days
Outcomes	PUs total numbers • Outcome type: dichotomous outcome • Direction: lower is better • Data value: change from baseline PU status: worse • Outcome type: dichotomous outcome • Direction: lower is better PU status: no change • Outcome type: dichotomous outcome • Data value: endpoint PU status: recovered • Outcome type: dichotomous outcome • Direction: higher is better PU status: new • Outcome type: dichotomous outcome • Direction: lower is better
Identification	**Sponsorship source:** Abbott Laboratory Representatives (Promedico Company) provided the enteral formulas **Country:** Israel **Setting:** Hospital, ICU **Authors:** Theilla, M., Singer, P., Cohen, J., DeKeyser, F. **Institution:** Department of General Intensive Care, Rabin Medical Center

Theilla 2007 *(Continued)*

Email: psinger@clalit.org.il

Address: Department of General Intensive Care, Rabin Medical Center, Beilinson Campus, Kaplan Street, Petah Tiqva 49100, Israel. Tel.: +972 3 9376521; fax: +972 3 9232333.

Notes

Theilla 2012

Study characteristics

Methods

Treatment study

Study design: RCT

Study grouping: parallel group

Participants

Baseline characteristics

Intervention group

- Sample size (randomized): 20
- Sample size (received intervention): 20
- Age, mean (SD), years: 49.3 (20.7)
- Male gender, No (%): 14 (70)
- Female gender, No (%): 6 (30)
- BMI, mean (SD): 28.3 (4.8)
- PUSH total score, mean (SD): 9.1 (2.8)
- PU stage 2, No: 14
- PU stage 3, No: 6

Control group

- Sample size (randomized): 20
- Sample size (received intervention): 20
- Age, mean (SD), years: 53.1 (19.3)
- Male gender, No (%): 13 (65)
- Female gender, No (%): 7 (35)
- BMI, mean (SD): 32.1 (9.9)
- PUSH total score, mean (SD): 9.3 (2.1)
- PU stage 2, No: 13
- PU stage 3, No: 7

Overall

- Sample size (randomized): 40
- Sample size (received intervention): 40
- Male gender, No (%): 27 (67.5)
- Female gender, No (%): 13 (32.5)
- PU stage 2, No: 27
- PU stage 3, No: 13

Included criteria: adult patients admitted to the general ICU; presented with or developed ≥ 1 stage 2(or higher) PU/s (i.e. damage to the epidermis extending at least into the dermis) according to the NPUAP classification; expected to be in need of nutritional support for at least 5 days.

Theilla 2012 *(Continued)*

	Excluded criteria: evidence of pre-existing impaired wound healing or abnormal immune status, e.g. patients receiving chemotherapy or treatment with > 0.25 mg/kg/d prednisone (or an iso-equivalent dose of other glucocorticoids). Significant intracranial haemorrhage was also an exclusion criterion. **Group differences:** no signficant group differences (PUs, PUSH scores, age, BMI), a higher percentage of positive CD18 lymphocytes in the control group (24.4 (SD 27.4) vs 48.1 (SD 38.1) % in the intervention group; P = 0.05)
Interventions	**Intervention characteristics** Intervention: mixed nutritional supplements (high energy, high protein, n-3 fatty acids and micronutrients) • Type of diet/supplementation: fish oil-and micronutrient-enriched formula • Macronutrients and micronutrients: formula per 100 mL enteral route: 10.5 g carbohydrates, 9.4 g fat, 6.2 g proteins, 0.46 g EPA, 0-4 g GLA, 850 mg vitamin C, 32 UI vitamin E, 667.8 UI vitamin A, 2.2 mg/1000 mL copper, 5.3 mg/100 mL manganese, 23.9 mg/1000 mL zinc; parenteral route: identical formula expect additional: 0.125-0.292 g EPA, 0.144-0.309 g DHA • Energy and amount of supplementation: determined by the measurement of resting energy expenditure as assessed by indirect calorimetry • Mode of feeding: where participants were unable to receive the full energy prescription via the enteral route, e.g. due to gastric paresis, enteral nutrition was supplemented with parenteral nutrition. • Intervention period: - Control: standard diet • Type of diets/supplementation: iso-nitrogenous formula • Macronutrients and micronutrients: formula per 100 mL enteral route: 15.4 g carbohydrates, 3.5 g fat, 4.4 g proteins, 0 g EPA, 0g GLA, 15.7-22.5 mg vitamin C, 2.3-3.4 UI vitamin E, 375.9 UI vitamin A, 1-1.5 mg/1000 mL copper, 2.6-3.7mg/100 mL manganese, 16.8 mg/1000 mL zinc • Energy and amount of supplementation: determined by the measurement of resting energy expenditure as assessed by indirect calorimetry • Mode of feeding: where participants were unable to receive the full energy prescription via the enteral route, e.g. due to gastric paresis, enteral nutrition was supplemented with parenteral nutrition. • Intervention period: -
Outcomes	PU healing: PUSH score • Outcome type: continuous outcome • Reporting: fully reported • Scale: PUSH • Range: 0-17 • Unit of measure: points • Direction: lower is better • Data value: change from baseline
Identification	**Sponsorship source:** no funding was received for this study. **Country:** Israel **Setting:** Hospital, ICU **Authors:** Theilla M, Schwartz B, Zimra Y, Shapiro H, Anbar R, Rabizadeh E, Cohen J, Singer P. **Institution:** Department of Hematology, Rabin Medical Center **Email:** psinger@clalit.org.il

Theilla 2012 *(Continued)*

	Address: Petah Tikva 49100, Israel
Notes	

Van Anholt 2010

Study characteristics	
Methods	**Treatment study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (received intervention): 22 • Age years, mean (SD): 76.2 (3.2) • Male gender, No (%): 8 (36.4) • BMI, mean (SD): 23.7 (1.0) • PU location: heel, No (%): 8 (36.4) • PU location: ischium, No (%): 2 (9.1) • PU location: sacrum, No (%): 8 (36.4) • PU location: trochanter, No (%): 4 (18.2) • PU stage 3, No (%): 17 (77.3) • PU stage 4, No (%): 5 (22.7) • Risk of malnutrition: low, No (%): 15 (68.2) • Risk of malnutrition: medium, No (%): 3 (13.6) • Risk of malnutrition: high, No (%): 4 (18.2) Control group • Sample size (received intervention): 21 • Age years, means (SD): 73.0 (3.3) • Male gender, No (%): 11 (52.4) • BMI, mean (SD): 25.8 (1.1) • PU location: heel, No (%): 8 (38.1) • PU location: ischium, No (%): 0 • PU location: sacrum, No (%): 8 (38.1) • PU location: trochanter, No (%): 5 (23.8) • PU stage 3, No (%): 14 (66.7) • PU stage 4, No (%): 7 (33.3) • Risk of malnutrition: low, No (%): 18 (85.7) • Risk of malnutrition: medium, No (%): 2 (9.5) • Risk of malnutrition: high, No (%): 1 (4.8) Overall • Sample size (randomized): 47 • Sample size (received intervention): 43 • Male gender, No (%): 19 (44.2) • PU location: heel, No (%): 16 (37.2)

Van Anholt 2010 *(Continued)*

- PU location: ischium, No (%): 2 (4.7)
- PU location: sacrum, No (%): 16 (37.2)
- PU location: trochanter, No (%): 9 (20.9)
- PU stage 3, No (%): 31 (72.1)
- PU stage 4, No (%): 12 (27.9)
- Risk of malnutrition: low, No (%): 33 (76.7)
- Risk of malnutrition: medium, No (%): 5 (11.6)
- Risk of malnutrition: high, No (%): 5 (11.6)

Included criteria: age 18-90 years; at least 1 stage 3-4 PU according to the revised EPUAP classification system; receiving standard care and a standard (institutional) diet without nutritional supplements for at least 2 weeks before the study

Excluded criteria: malnutrition (BMI < 18.5 for patients between 18-70 years old, BMI < 21 for patients > 70 years); severe medical conditions; no pressure-related ulcers (e.g. diabetic ulcers); life expectancy < 6 months; receiving palliative care; use of corticosteroids, and/or dietary restrictions, i.e. a protein-restricted diet

Group differences: no statistically significant differences between the groups, but slight differences in BMI (23.7 vs 25.8), weight (66.3 vs 75.6) and high risk for malnutrition (4 vs 1)

Interventions

Intervention characteristics

Intervention: mixed nutritional supplements (protein, arginine, zinc and antioxidants)

- Type of diet/supplementation: oral, high-energy nutritional supplement, enriched with arginine, antioxidants and other micronutrients
- Macronutrients and micronutrients: per serving: 28.4 g of carbohydrates, 20 g of protein, including 3 g of arginine, 7 g of fat, 238 mg of vitamin A, 250 mg of vitamin C, 38 mg of vitamin E (a-tocopherol equivalents), 1.5 mg of carotenoids, 9 mg of zinc, 64 mg of selenium, 1.35 mg of copper, and 200 mg of folic acid
- Energy: per serving 250 kcal
- Amount of supplementation: 3 times 200 mL daily
- Mode of feeding: enteral
- Intervention period: 56

Placebo

- Type of diet/supplementation: non-caloric flavoured placebo
- Macronutrients and micronutrients: -
- Energy (kcal/kg/d): -
- Amount of supplementation: 3 times 200 mL daily
- Mode of feeding: enteral
- Intervention period: 56

Outcomes

Ulcer size

- Outcome type: continuous outcome
- Reporting: fully reported
- Direction: lower is better
- Data value: endpoint

PUSH score

- Outcome type: continuous outcome
- Reporting: fully reported
- Direction: lower is better
- Data value: endpoint

Van Anholt 2010 *(Continued)*

Mean number of dressings

- Outcome type: continuous outcome

Persons who experience at least 1 adverse event

- Outcome type: adverse event
- Reporting: fully reported
- Direction: lower is better
- Data value: endpoint

Adverse effect: diarrhoea

- Outcome type: adverse event
- Reporting: fully reported
- Data value: endpoint

Adverse effect: nausea

- Outcome type: adverse event
- Reporting: fully reported
- Direction: lower is better
- Data value: endpoint

Adverse effect: vomiting

- Outcome type: adverse event
- Direction: lower is better
- Data value: endpoint

Adverse effects: constipation

- Outcome type: adverse event
- Reporting: fully reported
- Direction: lower is better
- Data value: endpoint

Adverse effect: dyspepsia

- Outcome type: adverse event
- Reporting: fully reported
- Direction: lower is better
- Data value: endpoint

Identification	**Sponsorship source:** sponsored by Nutricia Advanced Medical Nutrition **Country:** Czech Republic, Belgium, The Netherlands, and Curacao **Setting:** healthcare centers, hospitals, and long- term care facilities in 4 countries **Authors:** Van Anholt RD, Sobotka L, Meijer EP, Heyman H, Groen HW, Topinková E, Van Leen M, Schols JMGA **Institution:** Nutricia Advanced Medical Nutrition, Danone Research **Email:** rogier.vananholt@nutricia.com **Address:** -
Notes	

Wong 2014

Study characteristics	
Methods	**Treatment study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 12 • Sample size (received intervention): 11 • Age, mean (SEM), years: 79.4 (5.74) • Male gender, No (%): 3 (27.3) • Female gender, No (%): 8 (72.7) • Presence of diabetes, No (%): 3 (27) • Malnutrition screening scores (SGA)-A, No (%): 4 (36) • Malnutrition screening scores (SGA)-B, No (%): 6 (55) • Malnutrition screening scores (SGA)-C, No (%): 1 (9) • Feeding route - enteral, No (%): 7 (64) • Feeding route - oral, No (%): 4 (36) • Hospital length of stay, mean (SEM), days: 46.5 (16.7) • Weight, mean (SEM), kg: 44.35 (2.35) • PUSH score, mean (SEM): 12.41 (0.7) • PU area, mean (SEM), cm^2: 17.22 (5.24) • PU perimeter, mean (SEM), cm: 13.17 (2.23) • PU depth, mean (SEM), cm: 2.13 (0.48) • Total number of PUs, No: 18 • PU stage 3, No (%): 9 (50) • PU stage 4, No (%): 9 (50) • PU location - buttock, No (%): 2 (11.1) • PU location - decubitus, No (%): 1 (5.6) • PU location - foot, No (%): 3 (16.6) • PU location - hip, No (%): 2 (11.1) • PU location - iliac Crest, No (%): 0 (0) • PU location - malleolus, No (%): 1 (5.6) • PU location - sacral, No (%): 8 (44.4) • PU location - shin, No (%): 1 (5.6) Control group • Sample size (randomized): 14 • Sample size (received intervention): 12 • Age, mean (SEM), years: 75.5 (3.19) • Male gender, No (%): 6 (50) • Female gender, No (%): 6 (50) • Presence of diabetes, No (%): 3 (25) • Malnutrition screening scores (SGA)-A, No (%): 4 (33) • Malnutrition screening scores (SGA)-B, No (%): 6 (50) • Malnutrition screening scores (SGA)-C, No (%): 2 (17)

Wong 2014 *(Continued)*

- Feeding route - enteral, No (%): 6 (50)
- Feeding route - oral, No (%): 6 (50)
- Hospital length of stay, mean (SEM), days: 44.4 (15.1)
- Weight, mean (SEM), kg: 50.50 (4.40)
- PUSH score, mean (SEM): 12.38 (0.68)
- PU area, mean (SEM), cm^2: 20.56 (5.89)
- PU perimeter, mean (SEM), cm: 15.29 (2.17)
- PU depth, mean (SEM), cm: 2.17 (0.23)
- Total number of PUs, No: 16
- PU stage 2, No (%): 3 (18.8)
- PU stage 3, No (%): 6 (37.5)
- PU stage 4, No (%): 7 (43.7)
- PU location - buttock, No (%): 3 (18.8)
- PU location - foot, No (%): 2 (12.5)
- PU location - heel, No (%): 1 (6.2)
- PU location - iliac Crest, No (%): 1 (6.2)
- PU location - aacral, No (%): 9 (56.3)

Overall

- Sample size (randomized): 26
- Sample size (received intervention): 23
- Male gender, No (%): 9 (39.1)
- Female gender, No (%): 14 (60.9)
- Presence of diabetes, No (%): 6 (26.1)
- Malnutrition screening scores (SGA)-A, No (%): 8 (34.8)
- Malnutrition screening scores (SGA)-B, No (%): 12 (52.2)
- Malnutrition screening scores (SGA)-C, No (%): 3 (13.0)
- Feeding route - enteral, No (%): 13 (56.5)
- Feeding route - oral, No (%): 10 (43.5)

Included criteria: inpatients from Changi General Hospital with stage 2, 3 or 4 PU, who had no observable improvement in PU characteristics, were recruited into the study. The inclusion criteria were: patients with hospital stay of ≥ 2 weeks; able to attend follow-up outpatient clinics for PU assessment; and age > 21 years

Excluded criteria: patients with poorly controlled diabetes (HbA1c > 7.0%); on total parenteral nutrition; medically unstable upon admission to the hospital; on palliative care; admission with severe sepsis; length of stay in hospital ≤ 2 weeks and unable to attend outpatient follow-ups; on fluid restriction < 1L/d; requiring protein restriction; on other wound healing supplements such as vitamin C, vitamin A and zinc; presence of lower-extremity ulcers with untreated peripheral vascular disease, or deep tissue infection and/or requiring debridement of necrotic/sloughy tissue; unable to tolerate oral or enteral intake > 70% estimated energy requirements; and those who are unable to tolerate fluid intake 30 mL/kg body weight.

Group differences: no significant differences were observed between the 2 groups for anthropometric, biochemical, demographic, nutritional parameters and PU characteristics at baseline.

Interventions	**Intervention characteristics** Intervention: amino acid supplement (arginine, glutamine and HMB) Experimental group (ONS with arginine, glutamine and leucine) • Type of diet/supplementation: ONS (sachets mixing in water) with arginine, glutamine and leucine • Macronutrients and micronutrients: amino acid mixture sachets (Abound), each provides 7.0 g L-arginine, 7.0 g L-glutamin, 7.9 g carbohydrate, 1.5 g calcium HMB, 200 mg calcium, and orange

Wong 2014 *(Continued)*

	flavouring and nutrition according to nutritional requirements on energy and proteins (depending on the PU stage) • Energy (kcal/kg/d): each sachet provides 79 kcal (= 158 kcal/d additional) • Amount of supplementation: 2 sachets/d • Mode of feeding: either orally or via enteral tube feeding, by mixing in 240 mL of water • Intervention period: 2 weeks minimum Control group (placebo) • Type of diets/supplementation: placebo supplement (sachets mixed in water) matched for flavour • Macronutrients and micronutrients/energy: sachets with carbohydrate and calcium and nutrition according to nutritional requirements on energy and proteins (depending on the PU stage) • Amount of supplementation: 2 sachets/d • Mode of feeding: either orally or via enteral tube feeding, by mixing in 240 mL of water • Intervention period: 2 weeks minimum
Outcomes	Percentage decrease in PU area • Outcome type: continuous outcome Viable tissue • Outcome type: continuous outcome Death at 60 days • Outcome type: dichotomous outcome • Data value: endpoint PU healing rate/d • Outcome type: continuous outcome PU healing: PUSH score • Outcome type: continuous outcome
Identification	**Sponsorship source:** supported in part by Abbott Laboratories (Singapore) Pte Ltd. **Country:** Singapore **Setting:** Hospital **Authors:** Wong, A.; Chew, A.; Wang, C. M.; Ong, L.; Zhang, S. H.; Young, S. **Institution:** Department of Dietetics and Food Services, Changi General Hospital **Email:** alvin_wong@cgh.com.sg **Address:** -
Notes	

Yamanaka 2017

Study characteristics	
Methods	**Treatment study** **Study design:** RCT

Yamanaka 2017 *(Continued)*

Study grouping: parallel group

Participants

Baseline characteristics

Intervention group 1

- Sample size (randomized): 22
- Sample size (received intervention): 18
- Age, mean (SD), years: 76.8 (13.9)
- Male gender, No (%): 9 (50)
- Female gender, No (%): 9 (50)
- DESIGN-R scores prior to intervention, mean (SD): 14.1 (4.3)
- BMI, mean (SD): 18.8 (2.1)
- Braden Scale Score, mean (SD): 14.1 (3.8)

Intervention group 2

- Sample size (randomized): 22
- Sample size (received intervention): 17
- Age, mean (SD), years: 76.6 (12.0)
- Male gender, No (%): 7 (41.2)
- Female gender, No (%): 10 (58.8)
- DESIGN-R scores prior to intervention, mean (SD): 14.1 (5.6)
- BMI, mean (SD): 18.2 (2.7)
- Braden Scale Score, mean (SD): 12.9 (2.4)

Control group

- Sample size (randomized): 22
- Sample size (received intervention): 16
- Age, mean (SD), years: 79.9 (7.7)
- Male gender, No (%): 5 (31.3)
- Female gender, No (%): 11 (68.7)
- DESIGN-R scores prior to intervention, mean (SD): 15.9 (5.7)
- BMI, mean (SD): 18.5 (2.8)
- Braden Scale Score, mean (SD): 12.4 (2.8)

Overall

- Sample size (randomized): 66
- Sample size (received intervention): 51 (77.3)
- Male gender, No (%): 21 (41.2)
- Female gender, No (%): 30 (58.8)

Included criteria: receiving nasogastric tube, gastrostomy tube, or oral feeding who were able to consume 60% of the caloric requirement; PU depth, DESIGN-R 3-4; exudate, E0-E6; size, S3-S15; inflammation/infection, I0-I1 (local inflammation was included); granulation, G1-G5; necrotic tissue, N0-N3 (patients with necrotic tissue were included when yellow slough was ≤ 1/3, and those who satisfied the selection criteria after debridement were included); and pocket information, P0-P6 (those who satisfied the selection criteria after pockets were excised were included).

Excluded criteria: history of or current serious hepatic or renal dysfunction; current haemodialysis use; uncontrolled diabetes (hemoglobin A1c 8.0% (National Glycohemoglobin standardization Program value) or 7.6% (Japan Diabetes Society value)); C-reactive protein level 3.0 mg/dL due to systemic infection (patients with local inflammation were not excluded); the onset of aspiration pneumonia within the previous 1-month period; cancerous cachexia (diagnosis as refractory cachexia based on the international consensus); ulcers in the legs caused by venous insufficiency, arte-

Yamanaka 2017 *(Continued)*

	riosclerosis obliterans, severe diabetes, etc.; PUs that could not be evaluated and untreatable PUs; patients determined by attending physicians to be inappropriate for study inclusion. **Group differences:** no relevant detected
Interventions	**Intervention characteristics** Intervention 1: collagen supplement and micronutrients • Type of diet/supplementation: (oral) nutritional collagen peptide supplement • Macronutrients and micronutrients: 12.0 g protein (10.0 g collagen peptide) + standard hospital diet • Energy: + 80 kcal/d • Amount of supplementation: 125 mL once daily • Mode of feeding: enteral (both oral or tube) • Intervention period: 4 weeks Intervention 2: arginine and micronutrients • Type of diet/supplementation: (oral) nutritional arginine supplement • Macronutrients and micronutrients: 5.0 protein (2.5 g arginine) + standard hospital diet • Energy (kcal/kg/d): + 100 kcal/d • Amount of supplementation: 125 mL once daily • Mode of feeding: enteral (both oral or tube) • Intervention period: 4 weeks Control: standard diet • Type of diet/supplementation: standard hospital diet • Macronutrients and micronutrients: standard hospital diet • Energy (kcal/kg/d): - • Mode of feeding: enteral (both oral or tube) • Intervention period: 4 weeks
Outcomes	DESIGN-R scores • Outcome type: continuous outcome Adverse effect: diarrhoea • Outcome type: adverse event DESIGN-R score change-depth • Outcome type: continuous outcome DESIGN-R score change-size • Outcome type: continuous outcome DESIGN-R score change-infection • Outcome type: continuous outcome
Identification	**Sponsorship source:** Nutri Co., Ltd. **Country:** Japan **Setting:** hospital (In-patient-care) **Authors:** Yamanaka, H., Okada, S., Sanada, H.

Yamanaka 2017 *(Continued)*

Institution: Japanese Society for Parenteral and Enteral Nutrition and Japan Society of Pressure Ulcers

Email: wakakusa@wakakoukai.or.jp

Address: Department of Surgery, Wakakusa-Daiichi Hospital, 1-6 Wakakusa-cho, Higashi Osaka 579-8056, Japan

Notes	

Yu 2015

Study characteristics	
Methods	**Treatment study** **Study design:** RCT **Study grouping:** parallel group
Participants	**Baseline characteristics** Intervention group • Sample size (randomized): 38 • Sample size (received intervention): 38 • Age, mean (SD), years: 64.5 (10.9) • Male gender, No (%): 18 (47.4) • Female gender, No (%): 20 (52.6) • PU stages: stage 1, No: 4 • PU stages: stage 2, No: 19 • PU stages: stage 3, No: 11 • PU stages: stage 4, No: 4 Control group • Sample size (randomized): 38 • Sample size (received intervention): 38 • Age, mean (SD), years: 61.4 (10.1) • Male gender, No (%): 22 (57.9) • Female gender, No (%): 16 (42.1) • PU stages: stage 1, No: 6 • PU stages: stage 2, No: 16 • PU stages: stage 3, No: 14 • PU stages: stage 4, No: 2 Overall • Sample size (randomized): 76 • Sample size (received intervention): 76 • Male gender, No (%): 40 (52.6) • Female gender, No (%): 38 (47.4) • PU stages: stage 1, No: 10 • PU stages: stage 2, No: 35 • PU stages: stage 3, No: 25 • PU stages: stage 4, No: 6

Yu 2015 *(Continued)*

	Included criteria: patients with bedsores (PUs) provided consent and were cognitively intact **Excluded criteria:** severe liver, kidney, lung or heart disfunction; complete bowel obstruction; severe abdominal infection, peritonitis and ascites; extensive intestinal adhesions; emergency surgery, nauseous, vomiting or hemodynamic instability; gastrointestinal failure or decreased gastrointestinal tension **Group differences:** no statistically significant differences in gender, age and clinical classification **Additional PU treatment:** repositioning, infrared lamp irradiation, external use of QuFu ShengXin ointment, Hai Sheng powder and changing dressing
Interventions	**Intervention characteristics** Intervention: mixed nutritional supplements (high energy high protein and micronutrients) • Type of diet/supplementation: oral supplement (nutritional powder) • Macronutrients and micronutrients: - • Energy (kcal/kg/d): - • Amount of supplementation: 56 g/d • Mode of feeding: enteral • Intervention period: 20 days Control: standard diet • Type of diet/supplementation: standard hospital diet • Macronutrients and micronutrients: - • Energy (kcal/kg/d): - • Mode of feeding: enteral • Intervention period: 20 days
Outcomes	Complete healing • Outcome type: dichotomous outcome Unhealed PUs • Outcome type: dichotomous outcome
Identification	**Sponsorship source:** no information **Country:** China **Setting:** Hospital **Comments:** - **Authors:** Yu Yue, Liu Jun, Zhang NG Hongxing **Institution:** Natong Municipality TCM Hospital **Address:** Nantong Municipality TCM Hospital, Nantong 226000, China
Notes	

BMI: body mass index; **DESIGN-R:** depth, exudate, size, inflammation/infection, granulation tissue, and necrotic tisue rating; **DHA:** Docosahexaenoic acid; **EPA:** eicosapentaenoic acid; **EPUAP:** European Pressure Ulcer Advisory Panel; **GPA:** gammalinolenic acid; **HMB:** β-hydroxy-β-methylbutyrate; **ICU:** intensive care unit; **IU:** International Units; **MMSE:** Mini Mental State Examination; Mn: Manganese; **MNA:** Mini Nutritional Assessment; **NPUAP:** National Pressure Ulcer Advisory Panel; **OH scale:** Japanese patient intrinsic risk factor scale; self-sustainable ability to move unassisted, morbid bony prominence, edema, and articular contracture; **ONS:** oral nutritional supplements; **PaO_2/FIO_2 ratio:** ratio of partial pressure of oxygen in arterial blood by percentage of oxygen in a gas mixture; **PSST:** Pressure Sore Status

Tool; **PU:** pressure ulcer; **PUSH:** Pressure Ulcer Scale for Healing; **RCT:** randomized controlled trial; **REE:** Resting Energy Expenditure; **SD:** standard deviation; **SEM:** standard error of the mean; **SGA:** Subjective Global Assessment

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

Study	Reason for exclusion
Abbott 1968	Ineligible study design
Actrn 2021	PUs not measured
ACTRN12610000526077	PUs not measured
Alam 2021	Ineligible study design
Allen 2013	Ineligible study design
Anonymous 1971	Ineligible study design
Banks 1998	Ineligible study design
Bauer 2013	Focused on patients with different kinds of chronic wounds
Candela-Zamora 2010	Ineligible intervention
Cohen 1968	Ineligible study design
Collins 2002	Ineligible study design
Collins 2003	Ineligible study design
Collins 2004	Ineligible study design
Collins 2009	Ineligible study design
Cummins 2019	Ineligible study design
Delmi 1990	PU as side effects and not reporte/unclear
Doig 2013	PU incidence not measured - only invested time for PU care during intensive care stay
Gray 2003a	Ineligible study design
Gray 2003b	Ineligible study design
Gray 2003c	Ineligible study design
Gutman 2019	Ineligible study design
Harvey 2016	PU as side effects and not reported/unclear
Hunter 1971	Ineligible study design
IRCT20160914029817N8 2018	Ineligible intervention
IRCT20190824044595N 2020	Ineligible intervention

Study	Reason for exclusion
JPRN UMIN000012216	Ineligible study design
JPRN-UMIN000002072	PU not measured
JPRN-UMIN000022859	Ineligible study design
Landes 2016	Ineligible intervention
Langkamp-Henken 2000	PU not measured
Lauque 2004	PU as side effects and not reported/unclear
Lu 2019	Ineligible intervention
Lupianez Perez 2013	Ineligible intervention
Lupianez Perez 2017	Ineligible intervention
Mehl 2021	PU not measured
Natow 1983	Ineligible study design
NCT00135590	PU not measured
NCT00163007	PU not measured
NCT00502372	Study terminated
NCT00507650	PU not measured
NCT02711839	PU not measured
NCT03627910	PU not measured
NCT03658278	PU not measured
Olofsson 2007	Ineligible intervention
Olvera 2014	PU not measured
Omura 2020	Wrong study design
Pineda Juarez 2016	PU not measured
Posthauer 2005	Ineligible study design
Sakae 2014	Ineligible study design
Settel 1969	Ineligible intervention
Singer 2019	PU not measured
Starke 2011	PU as side effects and not reported/unclear
Thomas 1999	Ineligible study design

Study	Reason for exclusion
Vahabzadeh 2019	PU as side effects and not reported/unclear
Weismann 1974	Ineligible study design
Zhang 2021	Ineligible intervention

PU: pressure ulcer

Characteristics of studies awaiting classification *[ordered by study ID]*

Loreto Alvarez-Nebreda 2021

Methods	RCT
Participants	Patients ≥ 70 years with lower extremity fractures
Interventions	Intervention: preoperative complex carbohydrate drink Control: preoperative fasting
Outcomes	Perisurgical complications: delirium, infections, and PUs
Notes	

Ogawa 2021

Methods	RCT
Participants	Patients with cerebrovascular disease
Interventions	Intervention: enteral nutrition with EPAs Control: fed with an isonitrogenous and isocaloric control diet
Outcomes	Incidence frequency of PUs based on DESIGN-R
Notes	

Pertikov 2019

Methods	No information
Participants	Critically ill patients
Interventions	High-protein tube feeding
Outcomes	No information
Notes	

DESIGN-R: depth, exudate, size, inflammation/infection, granulation tissue, and necrotic tisue rating; **EPA:** eicosapentaenoic acid; **PU:** pressure ulcer; **RCT:** randomized controlled trial

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

CTRI/2019/07/020355

Study name	Impact of customized nutritional package on macro and micro nutrients (MAMN) in wound healing
Methods	Randomized, parallel-group trial
Participants	Adult patients (> 18 years) of both genders. Wound size ranging from 3 x 3 cm to 15 x15 cm. Wound duration > 10 days. Able to take food orally. Patient/family members can read and write Kannada or English.
Interventions	Intervention: customized nutritional package on macro and micro nutrients (MAMN) Control: routine treatment
Outcomes	Wound healing
Starting date	15 May 2019
Contact information	Latha T.: latharadhakrishna@gmail.com
Notes	Not yet recruiting

Hertig-Godeschalk 2021

Study name	Vitamin D supplementation in chronic spinal cord injury (VitD-SCI): study protocol for a randomised controlled trial
Methods	Randomized, placebo-controlled, double-blinded, parallel-group, superiority trial
Participants	Individuals with a spinal cord injury and a vitamin D insufficiency
Interventions	Monthly dosage of 24,000 IU or 48,000 IU vitamin D or a placebo for 12 months
Outcomes	Primary outcome • Vitamin D status (primary outcome) Secondary outcomes • Bone mineral density • Handgrip strength • Fatigue • Mood • Pain • Pressure injuries
Starting date	-
Contact information	hc.liwtton-nizidemtrops@kceulf.elleoj
Notes	

Irct20181111041611N

Study name	Evaluation of the efficacy of high protein high calorie diet include L-Arginine, L-Glutamine and ß-Hydroxy ß-Methylbutyrate on PUs and anthropometric indices in 20-50 years adults
Methods	RCT (parallel)
Participants	Patients with PUs, not being on special diets for the past 6 months
Interventions	Intervention: high-protein, high-calorie diet, along with 2 sachets/3 (noon and evening) of dietary supplements containing L-glutamine, L-arginine and HMB Control: high-protein, high-calorie diet with placebo consumption
Outcomes	PU status (PUSH Index)
Starting date	10/06/2020
Contact information	Mehnoosh Samadi: mehnoosh_samadi@yahoo.com
Notes	Not Recruiting

JPRN-UMIN000037811

Study name	Effects of nutritional intervention for high risk patients of pressure ulcer
Methods	Parallel RCT
Participants	Age minimum: 60 years-old, age maximum: 99 years-old Exclusion criteria: Patients with: • AST > 100 U/L or ALT > 100 U/L • HbA1c > 8.0 % • Creatinine > 2.0 mg/dL or BUN > 44 mg/dL • ASO • allergy to soy, gelatin, milk component • CT or RT treatment • other conditions not suitable for this study
Interventions	Polymeric formula: 900 Kcal/day Polymeric formula: 1200 Kcal/day Oligomeric formula: 900 Kcal/day Oligomeric formula: 1200 Kcal/day
Outcomes	• Abdominal circumference • Risk assessment for pressure ulcer • BW • Bony prominences • Skinfold thickness of iliac spine • PU incidence

JPRN-UMIN000037811 *(Continued)*

Starting date	24 April 2018
Contact information	Takehiko Ohura: t-ohura@mb.snowman.ne.jp
Notes	Status: recruiting

JPRN-UMIN000045099

Study name	Effectiveness of an oral nutritional supplement (Lipimain400) for malnourished older patients in rural community
Methods	Parallel RCT
Participants	Men and women aged ≥ 60 years
Interventions	ONS (120 g, 400 kcal, protein 5.2 g) every day for 3 months and nutritional education by a registered dietitian
Outcomes	Primary outcome • Nutritional status evaluated by anthropometry and MNA-SF Secondary • A risk score of PU development • PU status by DESIGN-R 2020
Starting date	27 May 2021
Contact information	Kunio Tsukada: care@zaitaku-jokusou.info
Notes	Status: recruiting

NCT03995407

Study name	100% whey protein based diet in enhancing pressure ulcer healing
Methods	Pilot RCT
Participants	Patients at any age, gender or ethnicity, admitted for subacute wound care, diagnosed with stage 3 or 4 PU, PU surface area > 4 cm^2
Interventions	Intervention: dietary supplement, Peptamen Control: usual care
Outcomes	• Percentage reduction in PU surface area • PUSH score
Starting date	20 June 2019
Contact information	JIANG SONG'EN, JEFFREY, St Luke's Hospital, Singapore

NCT03995407 *(Continued)*

Notes	

NCT05308862

Study name	PROSENIOR. Prevention of pressure ulcers, malnutrition, poor oral health and falls among older persons receiving municipal health care and are registered in the quality registry senior alert
Methods	Cluster-RCT
Participants	Nursing homes registering in Senior Alert, which is a national quality registry
Interventions	Intervention: workshops for nurse aides, registered nurses and managers working in nursing homes to develop an intervention together with the research group and then test it Control: continue with usual care
Outcomes	e.g. Risk assessments and prevention care interventions focusing on PUs
Starting date	4 April 022
Contact information	Malin Axelsson: malin.axelsson@mau.se
Notes	Not clear if the intervention focus is on nutrition

U1111-1216-6559

Study name	Dressings, nutritional supplementation and teaching of the patient and caregiver for the healing of bedsores
Methods	Open RCT with 3 arms
Participants	Patients ≥ 18 years of age; stage 2, 3 or 4 PUs up until 24 cm^2; BMI ≥ 18,5 kg/m^2 and < 30 kg/m^2 and therapeutic plan of hospitalization in the institution for at least 30 days. Caregivers ≥ 18 years of age.
Interventions	Intervention 1: topical therapy of the pressure injury with a calendula oil Intervention 2: injury treatment with calendula oil extract at 20% once a day (oral supplement) Control: placebo nutritional supplementation
Outcomes	Lesion area reduction rate
Starting date	08/01/2018
Contact information	Ana Carolina de Castro Mendonça Queiroz: carolinacmq@gmail.com
Notes	Study status: not yet recruiting

ALT: (alanine aminotransferase); **ASO:** antisense oligonucleotide; **AST:** aspartate aminotransferase; **BMI:** body mass index; **BUN:** blood urea nitrogen; **BW:** body weight; **CT:** chemotherapy; **DESIGN-R:** depth, exudate, size, inflammation/infection, granulation tissue, and necrotic tisue rating; **EER:** Existence energy rate; **HMB:** β-hydroxy-β-methylbutyrate; **IU:** international unit; **MNA-SF:** Mini Nutritional

Assessment-short form; **ONS:** oral nutritional supplement; **PU:** pressure ulcer; **PUSH:** Pressure Ulcer Scale for Healing; **RCT:** randomized controlled trial; **RT:** radiotherapy; **U/L**: Units per liter

RISK OF BIAS

Legend: Low risk of bias | High risk of bias | Some concerns

Risk of bias for analysis 1.1 Incidence of pressure ulcers

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Arias 2008	~	✗	✗	~	~	✗
Ek 1991	~	✗	✗	~	~	✗
Bourdel Marchasson 2000	✗	~	✓	✗	~	✗

Risk of bias for analysis 2.1 Incidence of pressure ulcers

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Houwing 2003	~	✓	✓	✓	~	~

Risk of bias for analysis 3.1 Incidence of pressure ulcers

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Derossi 2009	~	✗	~	~	~	✗

Risk of bias for analysis 4.1 Incidence of pressure ulcers

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Theilla 2007	~	✓	✓	✓	~	~

Risk of bias for analysis 5.1 Incidence of pressure ulcers

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Anbar 2014	✓	~	✓	~	✓	~
Botella Carretero 2008	✓	~	✓	~	~	~
Dennis 2005	✓	✓	✓	✗	~	✗
Hartgrink 1998	~	✓	~	~	~	~

Risk of bias for analysis 6.1 Incidence of pressure ulcers

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Craig 1998	~	~	~	~	~	~

Risk of bias for analysis 7.1 Pressure ulcers healed

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Ek 1991	~	✗	✗	~	~	✗

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Ohura 2011	✗	✗	✗	~	~	✗
Yu 2015	✗	~	✓	~	~	✗

Risk of bias for analysis 7.2 At least one adverse gastrointestinal effect

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Ohura 2011	✗	✗	✗	~	~	✗

Risk of bias for analysis 8.1 Pressure ulcers healed

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Cereda 2009	✗	✓	✓	✓	~	✗
Van Anholt 2010	~	✓	~	✓	✓	~

Risk of bias for analysis 8.4 At least one adverse gastrointestinal effect

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Van Anholt 2010	~	✓	~	✓	✓	~

Risk of bias for analysis 11.2 PUSH score

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Theilla 2012	~	~	✓	~	✓	~

Risk of bias for analysis 12.1 Pressure ulcers healed

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Chernoff 1990	~	~	✓	~	~	~

Risk of bias for analysis 12.5 Costs (EUR)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Pouyssegur 2015	✗	✗	✗	~	~	✗

Risk of bias for analysis 14.2 At least one adverse gastrointestinal effect

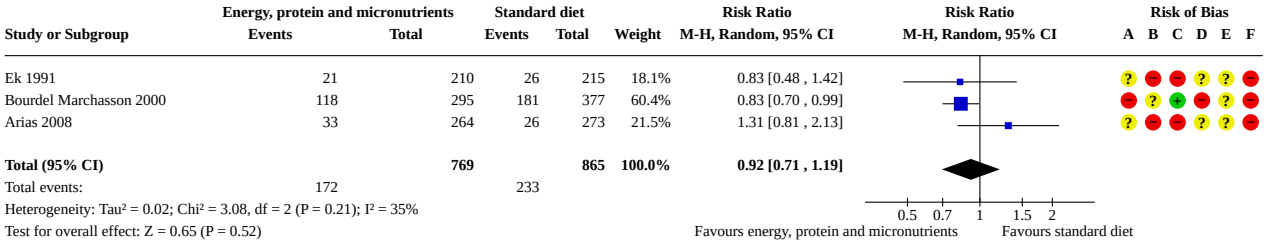
	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Miu 2021	✗	~	~	~	✓	✗

DATA AND ANALYSES

Comparison 1. Prevention: energy, protein and micronutrients versus standard diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Incidence of pressure ulcers	3	1634	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.71, 1.19]

Analysis 1.1. Comparison 1: Prevention: energy, protein and micronutrients versus standard diet, Outcome 1: Incidence of pressure ulcers

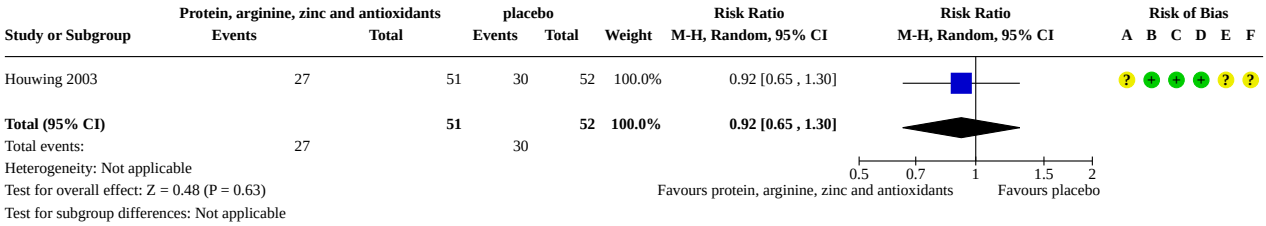


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2. Prevention: protein, arginine, zinc and antioxidants versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Incidence of pressure ulcers	1	103	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.65, 1.30]

Analysis 2.1. Comparison 2: Prevention: protein, arginine, zinc and antioxidants versus placebo, Outcome 1: Incidence of pressure ulcers

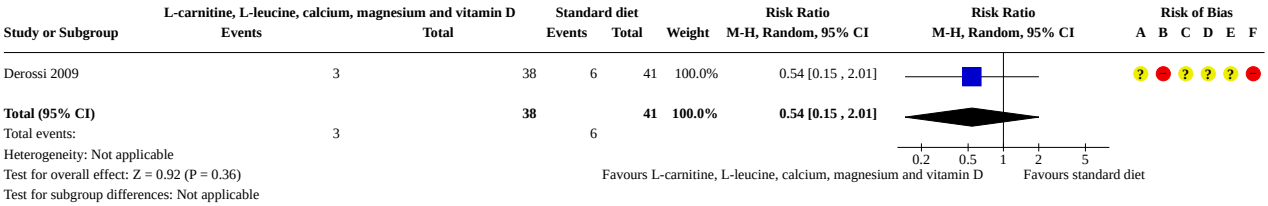


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 3. Prevention: L-carnitine, L-leucine, calcium, magnesium and vitamin D versus standard diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Incidence of pressure ulcers	1	79	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.15, 2.01]

Analysis 3.1. Comparison 3: Prevention: L-carnitine, L-leucine, calcium, magnesium and vitamin D versus standard diet, Outcome 1: Incidence of pressure ulcers

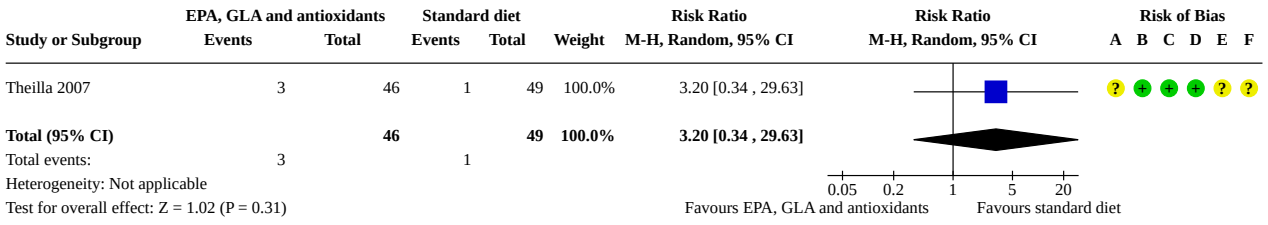


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 4. Prevention: EPA, GLA and antioxidants versus standard diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Incidence of pressure ulcers	1	95	Risk Ratio (M-H, Random, 95% CI)	3.20 [0.34, 29.63]

Analysis 4.1. Comparison 4: Prevention: EPA, GLA and antioxidants versus standard diet, Outcome 1: Incidence of pressure ulcers



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

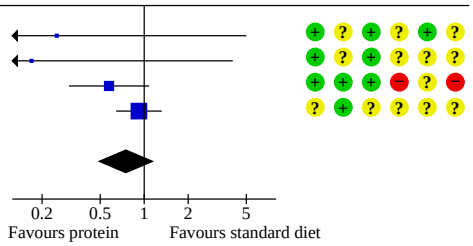
Comparison 5. Prevention: protein versus standard diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Incidence of pressure ulcers	4	4264	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.49, 1.14]
5.2 At least one adverse gastrointestinal effect	2	140	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.06, 7.96]

Analysis 5.1. Comparison 5: Prevention: protein versus standard diet, Outcome 1: Incidence of pressure ulcers

Study or Subgroup	Protein Events	Protein Total	Standard diet Events	Standard diet Total	Weight	Risk Ratio M-H, Random, 95% CI
Anbar 2014	0	22	2	28	1.9%	0.25 [0.01 , 5.00]
Botella Carretero 2008	0	60	1	30	1.7%	0.17 [0.01 , 4.04]
Dennis 2005	15	2016	26	2007	32.2%	0.57 [0.31 , 1.08]
Hartgrink 1998	25	48	30	53	64.1%	0.92 [0.64 , 1.32]
Total (95% CI)		**2146**		**2118**	**100.0%**	**0.75 [0.49 , 1.14]**
Total events:	40		59			

Heterogeneity: Tau² = 0.04; Chi² = 3.60, df = 3 (P = 0.31); I² = 17%
Test for overall effect: Z = 1.35 (P = 0.18)
Test for subgroup differences: Not applicable

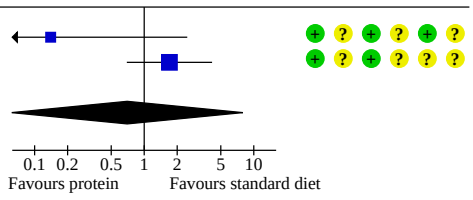


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.2. Comparison 5: Prevention: protein versus standard diet, Outcome 2: At least one adverse gastrointestinal effect

Study or Subgroup	Protein Events	Protein Total	Standard diet Events	Standard diet Total	Weight	Risk Ratio M-H, Random, 95% CI
Anbar 2014	0	22	4	28	35.6%	0.14 [0.01 , 2.47]
Botella Carretero 2008	17	60	5	30	64.4%	1.70 [0.69 , 4.16]
Total (95% CI)		**82**		**58**	**100.0%**	**0.70 [0.06 , 7.96]**
Total events:	17		9			

Heterogeneity: Tau² = 2.18; Chi² = 2.86, df = 1 (P = 0.09); I² = 65%
Test for overall effect: Z = 0.29 (P = 0.77)
Test for subgroup differences: Not applicable

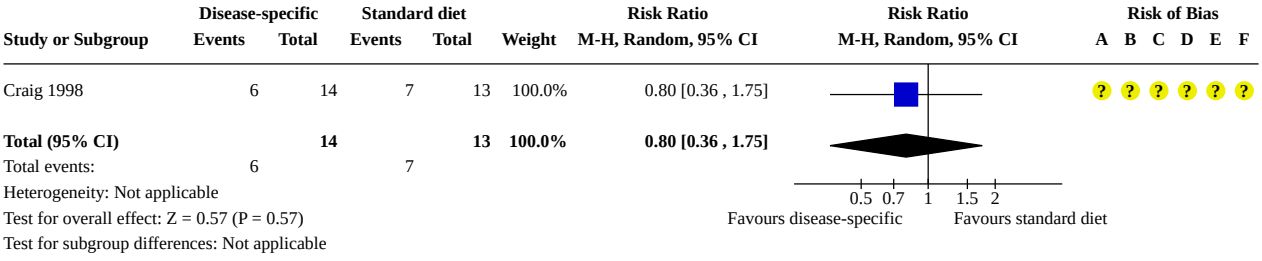


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 6. Prevention: disease-specific versus standard diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Incidence of pressure ulcers	1	27	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.36, 1.75]

Analysis 6.1. Comparison 6: Prevention: disease-specific versus standard diet, Outcome 1: Incidence of pressure ulcers



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

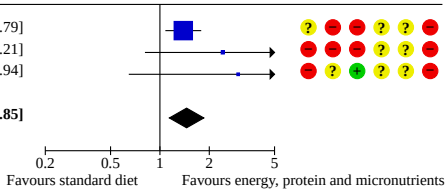
Comparison 7. Treatment: energy, protein and micronutrients versus standard diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Pressure ulcers healed	3	577	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.14, 1.85]
7.2 At least one adverse gastrointestinal effect	1	60	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.59, 4.33]

Analysis 7.1. Comparison 7: Treatment: energy, protein and micronutrients versus standard diet, Outcome 1: Pressure ulcers healed

Study or Subgroup	Energy, protein and micronutrients Events	Total	Standard diet Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ek 1991	94	225	68	226	92.6%	1.39 [1.08 , 1.79]
Ohura 2011	7	21	4	29	4.9%	2.42 [0.81 , 7.21]
Yu 2015	6	38	2	38	2.5%	3.00 [0.65 , 13.94]
Total (95% CI)		**284**		**293**	**100.0%**	**1.45 [1.14 , 1.85]**
Total events:	107		74			

Heterogeneity: Tau² = 0.00; Chi² = 1.83, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 3.03 (P = 0.002)
Test for subgroup differences: Not applicable

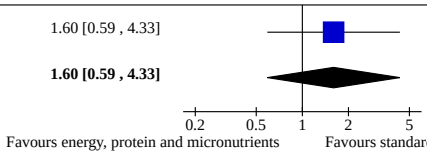


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.2. Comparison 7: Treatment: energy, protein and micronutrients versus standard diet, Outcome 2: At least one adverse gastrointestinal effect

Study or Subgroup	Energy, protein and micronutrients Events	Total	Standard diet Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ohura 2011	8	30	5	30	100.0%	1.60 [0.59 , 4.33]
Total (95% CI)		**30**		**30**	**100.0%**	**1.60 [0.59 , 4.33]**
Total events:	8		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

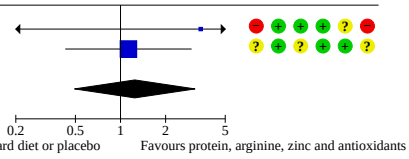
Comparison 8. Treatment: protein, arginine, zinc and antioxidants versus standard diet or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Pressure ulcers healed	2	61	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.49, 3.15]
8.2 Change in pressure ulcer area (cm^2)	2	71	Mean Difference (IV, Random, 95% CI)	-2.00 [-4.54, 0.53]
8.3 PUSH score	3	80	Mean Difference (IV, Random, 95% CI)	-2.71 [-4.82, -0.61]
8.4 At least one adverse gastrointestinal effect	1	43	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.77, 1.79]

Analysis 8.1. Comparison 8: Treatment: protein, arginine, zinc and antioxidants versus standard diet or placebo, Outcome 1: Pressure ulcers healed

Study or Subgroup	Protein, arginine, zinc and antioxidants Events	Total	Standard diet or placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cereda 2009	1	13	0	15	8.8%	3.43 [0.15 , 77.58]
Van Anholt 2010	6	17	5	16	91.2%	1.13 [0.43 , 2.98]
Total (95% CI)		**30**		**31**	**100.0%**	**1.25 [0.49 , 3.15]**
Total events:	7		5			

Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.46 (P = 0.64)
Test for subgroup differences: Not applicable

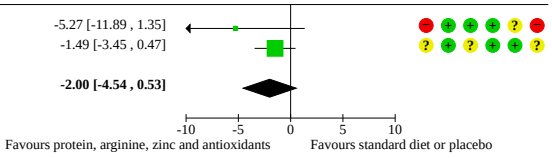


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 8.2. Comparison 8: Treatment: protein, arginine, zinc and antioxidants versus standard diet or placebo, Outcome 2: Change in pressure ulcer area (cm²)

Study or Subgroup	Protein, arginine, zinc and antioxidants Mean [cm²]	SD [cm²]	Total	Standard diet or placebo Mean [cm²]	SD [cm²]	Total	Weight	Mean Difference IV, Random, 95% CI [cm²]
Cereda 2009	7.01	8.35	13	12.28	9.52	15	13.6%	-5.27 [-11.89 , 1.35]
Van Anholt 2010	1.85	3.517812	22	3.34	3.0245	21	86.4%	-1.49 [-3.45 , 0.47]
Total (95% CI)			**35**			**36**	**100.0%**	**-2.00 [-4.54 , 0.53]**

Heterogeneity: Tau² = 0.94; Chi² = 1.15, df = 1 (P = 0.28); I² = 13%
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable

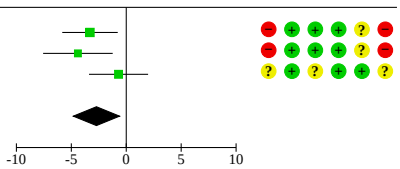


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 8.3. Comparison 8: Treatment: protein, arginine, zinc and antioxidants versus standard diet or placebo, Outcome 3: PUSH score

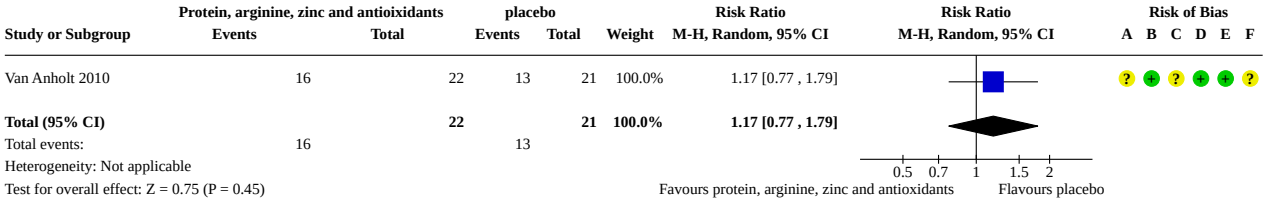
Study or Subgroup	Protein, arginine, zinc and antioxidants Mean	SD	Total	Standard diet or placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cereda 2009	7.4	3.4	13	10.7	3.4	15	37.0%	-3.30 [-5.83 , -0.77]
Desneves 2005	2.6	1.2	4	7	3.354102	5	28.4%	-4.40 [-7.57 , -1.23]
Van Anholt 2010	5.28	4.502799	22	5.98	4.490924	21	34.6%	-0.70 [-3.39 , 1.99]
Total (95% CI)			**39**			**41**	**100.0%**	**-2.71 [-4.82 , -0.61]**

Heterogeneity: Tau² = 1.46; Chi² = 3.45, df = 2 (P = 0.18); I² = 42%
Test for overall effect: Z = 2.53 (P = 0.01)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 8.4. Comparison 8: Treatment: protein, arginine, zinc and antioxidants versus standard diet or placebo, Outcome 4: At least one adverse gastrointestinal effect



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

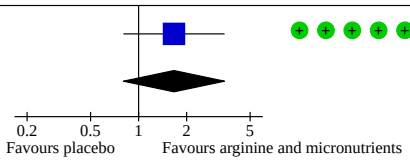
Comparison 9. Treatment: arginine and micronutrients versus standard diet or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Pressure ulcers healed	1	200	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.80, 3.46]
9.2 Change in pressure ulcer area (cm^2)	1	31	Mean Difference (IV, Random, 95% CI)	-3.25 [-7.19, 0.69]
9.3 Change in pressure ulcer area (percentage)	2	231	Mean Difference (IV, Random, 95% CI)	-15.80 [-25.11, -6.48]
9.4 Change in PUSH score	1	31	Mean Difference (IV, Random, 95% CI)	-0.48 [-3.80, 2.84]
9.5 DESIGN-R score	1	29	Mean Difference (IV, Random, 95% CI)	-1.60 [-9.53, 6.33]
9.6 At least one adverse gastrointestinal effects	3	282	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.36, 6.64]
9.7 Costs (EUR)	1	138	Mean Difference (IV, Random, 95% CI)	39.40 [27.57, 51.23]
9.8 Acceptability: non adherence	1	49	Risk Ratio (M-H, Random, 95% CI)	15.60 [0.94, 259.00]

Analysis 9.1. Comparison 9: Treatment: arginine and micronutrients versus standard diet or placebo, Outcome 1: Pressure ulcers healed

Study or Subgroup	Arginine and micronutrients Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Cereda 2015	17	101	10	99	100.0%	1.67 [0.80 , 3.46]	+ + + + + +
Total (95% CI)		**101**		**99**	**100.0%**	**1.67 [0.80 , 3.46]**	
Total events:	17		10				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.37 (P = 0.17)
Test for subgroup differences: Not applicable

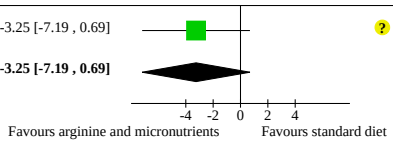


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.2. Comparison 9: Treatment: arginine and micronutrients versus standard diet or placebo, Outcome 2: Change in pressure ulcer area (cm²)

Study or Subgroup	Arginine and micronutrients Mean [cm²]	SD [cm²]	Total	Standard diet Mean [cm²]	SD [cm²]	Total	Weight	Mean Difference IV, Random, 95% CI [cm²]	Risk of Bias A B C D E F
Banks 2016	-3.7	6.6	14	-0.45	3.98	17	100.0%	-3.25 [-7.19 , 0.69]	? ? − ? + −
Total (95% CI)			**14**			**17**	**100.0%**	**-3.25 [-7.19 , 0.69]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.62 (P = 0.11)
Test for subgroup differences: Not applicable

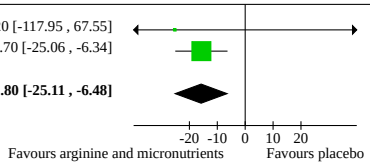


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.3. Comparison 9: Treatment: arginine and micronutrients versus standard diet or placebo, Outcome 3: Change in pressure ulcer area (percentage)

Study or Subgroup	Arginine and micronutrients Mean [%]	SD [%]	Total	Placebo Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Random, 95% CI [%]	Risk of Bias A B C D E F
Banks 2016	-28.52	108.43	14	-3.32	154.25	17	1.0%	-25.20 [-117.95 , 67.55]	? ? − ? + −
Cereda 2015	-60.9	33.432526	101	-45.2	34.094359	99	99.0%	-15.70 [-25.06 , -6.34]	+ + + + + +
Total (95% CI)			**115**			**116**	**100.0%**	**-15.80 [-25.11 , -6.48]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 3.32 (P = 0.0009)
Test for subgroup differences: Not applicable

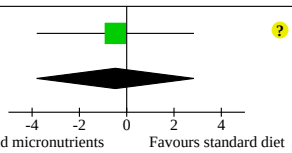


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.4. Comparison 9: Treatment: arginine and micronutrients versus standard diet or placebo, Outcome 4: Change in PUSH score

Study or Subgroup	Arginine and micronutrients Mean	SD	Total	Standard diet Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Banks 2016	-4.03	4.3	14	-3.55	5.14	17	100.0%	-0.48 [-3.80 , 2.84]
Total (95% CI)			**14**			**17**	**100.0%**	**-0.48 [-3.80 , 2.84]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable

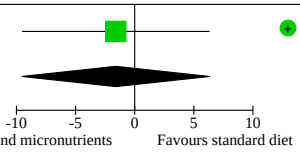


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.5. Comparison 9: Treatment: arginine and micronutrients versus standard diet or placebo, Outcome 5: DESIGN-R score

Study or Subgroup	Arginine and micronutrients Mean	SD	Total	Standard diet Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Yamanaka 2017	13.2	13.4	14	14.8	7.3	15	100.0%	-1.60 [-9.53 , 6.33]
Total (95% CI)			**14**			**15**	**100.0%**	**-1.60 [-9.53 , 6.33]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable

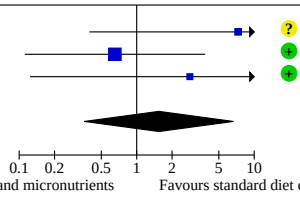


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.6. Comparison 9: Treatment: arginine and micronutrients versus standard diet or placebo, Outcome 6: At least one adverse gastrointestinal effects

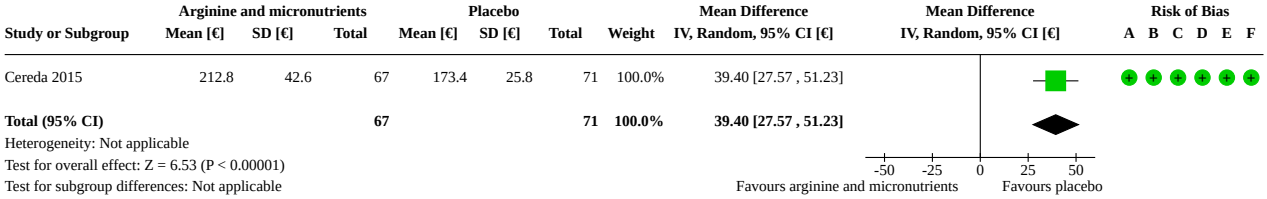
Study or Subgroup	Arginine and micronutrients Events	Total	Standard diet or placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Banks 2016	3	24	0	25	23.3%	7.28 [0.40 , 133.89]
Cereda 2015	2	101	3	99	56.3%	0.65 [0.11 , 3.83]
Yamanaka 2017	1	17	0	16	20.3%	2.83 [0.12 , 64.89]
Total (95% CI)		**142**		**140**	**100.0%**	**1.54 [0.36 , 6.64]**
Total events:	6		3			

Heterogeneity: Tau² = 0.17; Chi² = 2.20, df = 2 (P = 0.33); I² = 9%
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



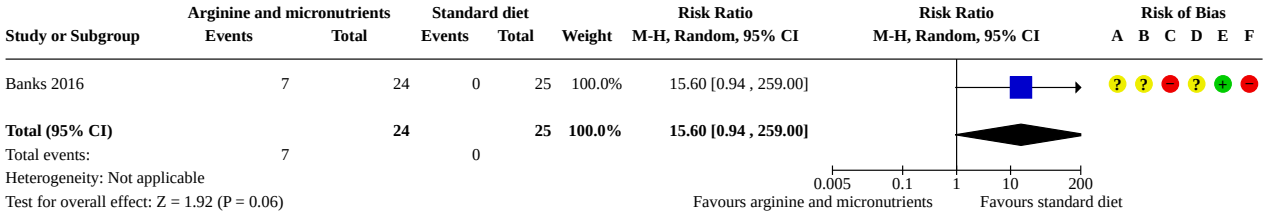
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.7. Comparison 9: Treatment: arginine and micronutrients versus standard diet or placebo, Outcome 7: Costs (EUR)



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.8. Comparison 9: Treatment: arginine and micronutrients versus standard diet or placebo, Outcome 8: Acceptability: non adherence



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

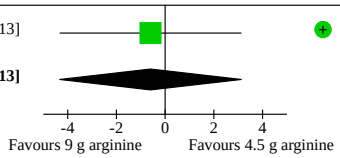
Comparison 10. Treatment: different doses of arginine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 PUSH score	1	22	Mean Difference (IV, Random, 95% CI)	-0.60 [-4.33, 3.13]
10.2 At least one side effect	1	29	Risk Ratio (M-H, Random, 95% CI)	2.81 [0.12, 63.83]
10.3 Acceptability: non adherence	1	23	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.08, 15.41]

Analysis 10.1. Comparison 10: Treatment: different doses of arginine, Outcome 1: PUSH score

Study or Subgroup	9 g arginine Mean	SD	Total	4.5 g arginine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Leigh 2012	4.9	4.4	10	5.5	4.5	12	100.0%	-0.60 [-4.33 , 3.13]
Total (95% CI)			**10**			**12**	**100.0%**	**-0.60 [-4.33 , 3.13]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)
Test for subgroup differences: Not applicable

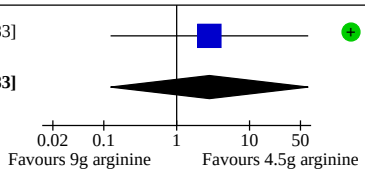


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 10.2. Comparison 10: Treatment: different doses of arginine, Outcome 2: At least one side effect

Study or Subgroup	9 g arginine Events	Total	4.5 g arginine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Leigh 2012	1	15	0	14	100.0%	2.81 [0.12 , 63.83]
Total (95% CI)		**15**		**14**	**100.0%**	**2.81 [0.12 , 63.83]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Not applicable

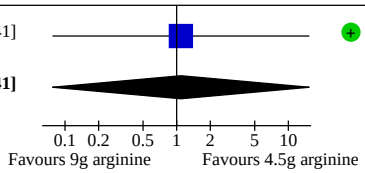


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 10.3. Comparison 10: Treatment: different doses of arginine, Outcome 3: Acceptability: non adherence

Study or Subgroup	9 g arginine Events	Total	4.5 g arginine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Leigh 2012	1	11	1	12	100.0%	1.09 [0.08 , 15.41]
Total (95% CI)		**11**		**12**	**100.0%**	**1.09 [0.08 , 15.41]**
Total events:	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

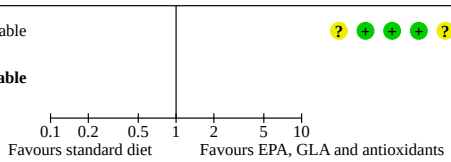
Comparison 11. Treatment: EPA, GLA and antioxidants versus standard diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Pressure ulcers healed	1	95	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.2 PUSH score	1	40	Mean Difference (IV, Random, 95% CI)	-1.35 [-5.78, 3.08]

Analysis 11.1. Comparison 11: Treatment: EPA, GLA and antioxidants versus standard diet, Outcome 1: Pressure ulcers healed

Study or Subgroup	EPA, GLA and antioxidants Events	Total	Standard diet Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Theilla 2007	0	46	0	49		Not estimable	? + + + ? ?
Total (95% CI)		**46**		**49**		**Not estimable**	
Total events:	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

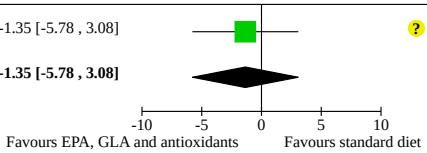


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 11.2. Comparison 11: Treatment: EPA, GLA and antioxidants versus standard diet, Outcome 2: PUSH score

Study or Subgroup	EPA, GLA and antioxidants Mean	SD	Total	Standard diet Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
Theilla 2012	9.4	3.72	20	10.75	9.4	20	100.0%	-1.35 [-5.78 , 3.08]	? ? + ? + ?
Total (95% CI)			**20**			**20**	**100.0%**	**-1.35 [-5.78 , 3.08]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable



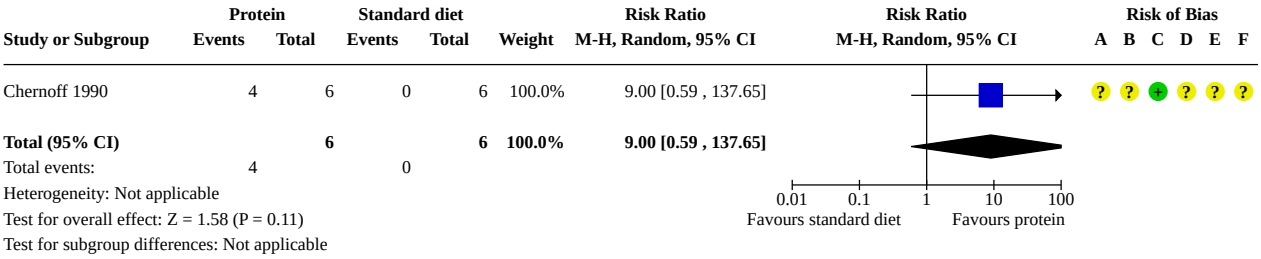
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 12. Treatment: protein versus standard diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Pressure ulcers healed	1	12	Risk Ratio (M-H, Random, 95% CI)	9.00 [0.59, 137.65]

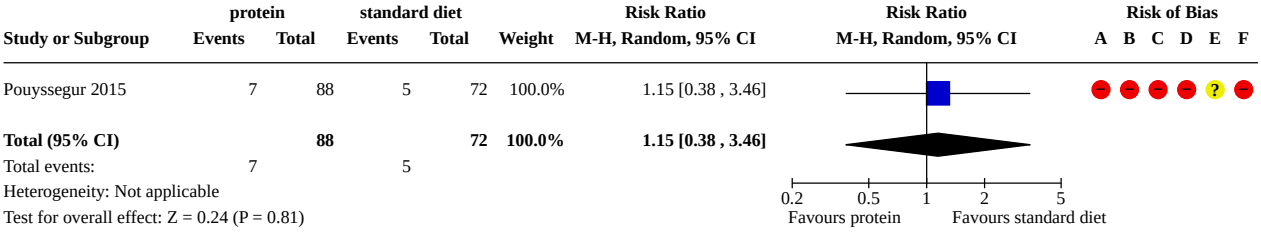
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.2 Pressure ulcer episodes	1	160	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.38, 3.46]
12.3 PUSH score	1	9	Mean Difference (IV, Random, 95% CI)	-1.00 [-2.76, 0.76]
12.4 Diarrhoea episodes	1	152	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.02, 1.22]
12.5 Costs (EUR)	1	175	Mean Difference (IV, Random, 95% CI)	-191.00 [-240.63, -141.37]

Analysis 12.1. Comparison 12: Treatment: protein versus standard diet, Outcome 1: Pressure ulcers healed



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 12.2. Comparison 12: Treatment: protein versus standard diet, Outcome 2: Pressure ulcer episodes

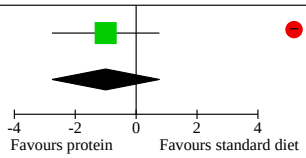


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 12.3. Comparison 12: Treatment: protein versus standard diet, Outcome 3: PUSH score

Study or Subgroup	Protein Mean	Protein SD	Protein Total	Standard diet Mean	Standard diet SD	Standard diet Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
Desneves 2005	6	1.2	4	7	1.5	5	100.0%	-1.00 [-2.76 , 0.76]	− + + + ? −
Total (95% CI)			**4**			**5**	**100.0%**	**-1.00 [-2.76 , 0.76]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable

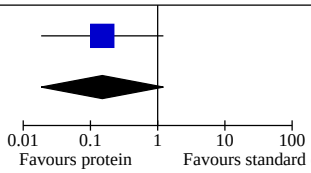


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 12.4. Comparison 12: Treatment: protein versus standard diet, Outcome 4: Diarrhoea episodes

Study or Subgroup	Protein Events	Protein Total	Standard diet Events	Standard diet Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Pouyssegur 2015	1	80	6	72	100.0%	0.15 [0.02 , 1.22]	− − − − ? −
Total (95% CI)		**80**		**72**	**100.0%**	**0.15 [0.02 , 1.22]**	
Total events:	1		6				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.78 (P = 0.08)
Test for subgroup differences: Not applicable

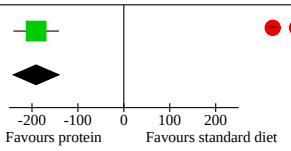


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 12.5. Comparison 12: Treatment: protein versus standard diet, Outcome 5: Costs (EUR)

Study or Subgroup	Protein Mean [€]	Protein SD [€]	Protein Total	Standard diet Mean [€]	Standard diet SD [€]	Standard diet Total	Weight	Mean Difference IV, Random, 95% CI [€]	Risk of Bias A B C D E F
Pouyssegur 2015	885	155	88	1076	179	87	100.0%	-191.00 [-240.63 , -141.37]	− − − ? ? −
Total (95% CI)			**88**			**87**	**100.0%**	**-191.00 [-240.63 , -141.37]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 7.54 (P < 0.00001)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

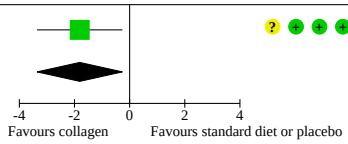
Comparison 13. Treatment: collagen versus standard diet or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Change in pressure ulcer area (cm^2)	1	74	Mean Difference (IV, Random, 95% CI)	-1.81 [-3.36, -0.26]
13.2 PUSH score	2	183	Mean Difference (IV, Random, 95% CI)	-1.00 [-3.13, 1.14]
13.3 DESIGN-R score	1	32	Mean Difference (IV, Random, 95% CI)	-6.00 [-10.76, -1.24]
13.4 At least one adverse gastrointestinal effect	2	154	Risk Ratio (M-H, Random, 95% CI)	2.69 [0.33, 22.30]

Analysis 13.1. Comparison 13: Treatment: collagen versus standard diet or placebo, Outcome 1: Change in pressure ulcer area (cm^2)

Study or Subgroup	Collagen Mean [cm^2]	Collagen SD [cm^2]	Collagen Total	Standard diet or placebo Mean [cm^2]	Standard diet or placebo SD [cm^2]	Standard diet or placebo Total	Weight	Mean Difference IV, Random, 95% CI [cm^2]	Risk of Bias A B C D E F
Sugihara 2018	3.19	2.88	35	5	3.88	39	100.0%	-1.81 [-3.36 , -0.26]	? + + + + ?
Total (95% CI)			**35**			**39**	**100.0%**	**-1.81 [-3.36 , -0.26]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 2.29 (P = 0.02)
Test for subgroup differences: Not applicable

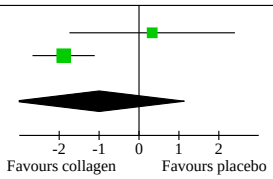


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 13.2. Comparison 13: Treatment: collagen versus standard diet or placebo, Outcome 2: PUSH score

Study or Subgroup	Collagen Mean	Collagen SD	Collagen Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
Lee 2006	3.55	4.66	44	3.22	4.11	27	40.2%	0.33 [-1.74 , 2.40]	- ? ? + ? -
Sugihara 2018	7.370959	1.834958	73	9.26	2.09	39	59.8%	-1.89 [-2.67 , -1.11]	? + + + + ?
Total (95% CI)			**117**			**66**	**100.0%**	**-1.00 [-3.13 , 1.14]**	

Heterogeneity: Tau² = 1.82; Chi² = 3.86, df = 1 (P = 0.05); I² = 74%
Test for overall effect: Z = 0.92 (P = 0.36)
Test for subgroup differences: Not applicable

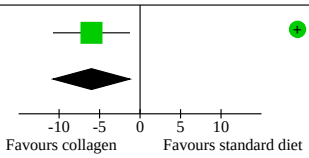


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 13.3. Comparison 13: Treatment: collagen versus standard diet or placebo, Outcome 3: DESIGN-R score

Study or Subgroup	Collagen Mean	Collagen SD	Collagen Total	Standard diet Mean	Standard diet SD	Standard diet Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
Yamanaka 2017	8.8	6.3	17	14.8	7.3	15	100.0%	-6.00 [-10.76 , -1.24]	+ + + + ? ?
Total (95% CI)			**17**			**15**	**100.0%**	**-6.00 [-10.76 , -1.24]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 2.47 (P = 0.01)
Test for subgroup differences: Not applicable

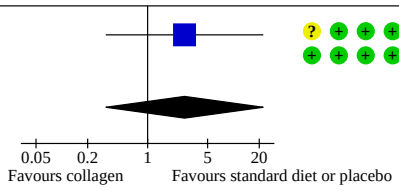


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 13.4. Comparison 13: Treatment: collagen versus standard diet or placebo, Outcome 4: At least one adverse gastrointestinal effect

Study or Subgroup	Collagen Events	Collagen Total	Standard diet or placebo Events	Standard diet or placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Sugihara 2018	5	78	1	42	100.0%	2.69 [0.33 , 22.30]	? + + + + ?
Yamanaka 2017	0	18	0	16		Not estimable	+ + + + ? ?
Total (95% CI)		**96**		**58**	**100.0%**	**2.69 [0.33 , 22.30]**	
Total events:	5		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)
Test for subgroup differences: Not applicable

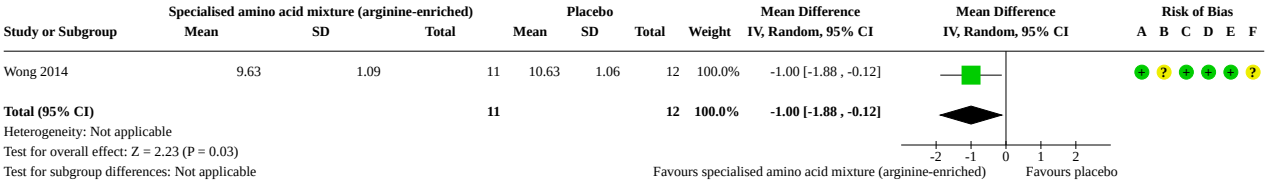


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 14. Treatment: specialised amino acid mixture (arginine-enriched) versus standard diet or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 PUSH score	1	23	Mean Difference (IV, Random, 95% CI)	-1.00 [-1.88, -0.12]
14.2 At least one adverse gastrointestinal effect	1	87	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 14.1. Comparison 14: Treatment: specialised amino acid mixture (arginine-enriched) versus standard diet or placebo, Outcome 1: PUSH score



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 14.2. Comparison 14: Treatment: specialised amino acid mixture (arginine-enriched) versus standard diet or placebo, Outcome 2: At least one adverse gastrointestinal effect

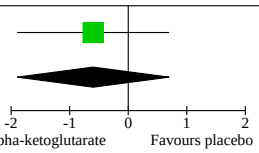
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 15. Treatment: ornithine alpha-ketoglutarate versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Change in pressure ulcer area (cm^2)	1	93	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.90, 0.70]
15.2 Change in pressure ulcer area (percentage)	1	93	Mean Difference (IV, Random, 95% CI)	-5.50 [-34.04, 23.04]
15.3 Side effects	1	160	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.55, 2.20]

Analysis 15.1. Comparison 15: Treatment: ornithine alpha-ketoglutarate versus placebo, Outcome 1: Change in pressure ulcer area (cm²)

Study or Subgroup	Ornithine alpha-ketoglutarate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
Meaume 2009	-2.3	4.2	47	-1.7	1.7	46	100.0%	-0.60 [-1.90 , 0.70]		+ + + ? ? ?
Total (95% CI)			**47**			**46**	**100.0%**	**-0.60 [-1.90 , 0.70]**		

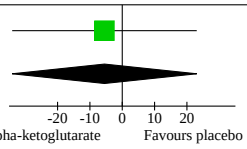


Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.36)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 15.2. Comparison 15: Treatment: ornithine alpha-ketoglutarate versus placebo, Outcome 2: Change in pressure ulcer area (percentage)

Study or Subgroup	Ornithine alpha-ketoglutarate Mean [%]	SD [%]	Total	Placebo Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Random, 95% CI [%]	Mean Difference IV, Random, 95% CI [%]	Risk of Bias A B C D E F
Meaume 2009	-59.5	71.4	47	-54	69	46	100.0%	-5.50 [-34.04 , 23.04]		+ + + ? ? ?
Total (95% CI)			**47**			**46**	**100.0%**	**-5.50 [-34.04 , 23.04]**		

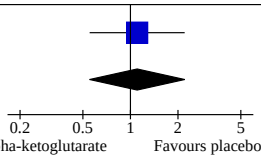


Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.71)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 15.3. Comparison 15: Treatment: ornithine alpha-ketoglutarate versus placebo, Outcome 3: Side effects

Study or Subgroup	Ornithine alpha-ketoglutarate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Meaume 2009	15	85	12	75	100.0%	1.10 [0.55 , 2.20]		+ + + ? ? ?
Total (95% CI)		**85**		**75**	**100.0%**	**1.10 [0.55 , 2.20]**		
Total events:	15		12					



Heterogeneity: Not applicable
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

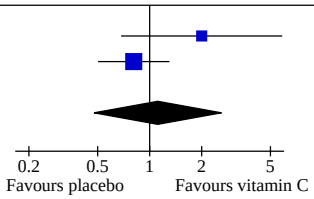
Comparison 16. Treatment: vitamin C versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Pressure ulcers healed	2	108	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.48, 2.60]
16.2 Change in pressure ulcer area (percentage)	1	20	Mean Difference (IV, Random, 95% CI)	-41.30 [-62.10, -20.50]

Analysis 16.1. Comparison 16: Treatment: vitamin C versus placebo, Outcome 1: Pressure ulcers healed

Study or Subgroup	Vitamin C Events	Vitamin C Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Taylor 1974	6	10	3	10	35.3%	2.00 [0.68 , 5.85]
Ter Riet 1995	17	43	22	45	64.7%	0.81 [0.50 , 1.30]
Total (95% CI)		**53**		**55**	**100.0%**	**1.11 [0.48 , 2.60]**
Total events:	23		25			

Heterogeneity: Tau² = 0.23; Chi² = 2.29, df = 1 (P = 0.13); I² = 56%
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Not applicable

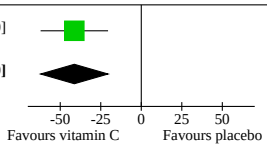


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 16.2. Comparison 16: Treatment: vitamin C versus placebo, Outcome 2: Change in pressure ulcer area (percentage)

Study or Subgroup	Vitamin C Mean [%]	Vitamin C SD [%]	Vitamin C Total	Placebo Mean [%]	Placebo SD [%]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [%]
Taylor 1974	-84	24.03331	10	-42.7	23.432477	10	100.0%	-41.30 [-62.10 , -20.50]
Total (95% CI)			**10**			**10**	**100.0%**	**-41.30 [-62.10 , -20.50]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.89 (P < 0.0001)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

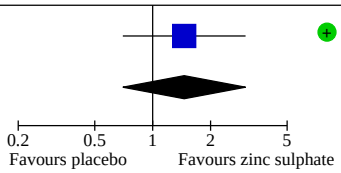
Comparison 17. Treatment: zinc sulphate versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Pressure ulcers healed	1	13	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.70, 3.04]
17.2 Change in pressure ulcer volume (mL)	1	18	Mean Difference (IV, Random, 95% CI)	4.10 [-9.25, 17.45]

Analysis 17.1. Comparison 17: Treatment: zinc sulphate versus placebo, Outcome 1: Pressure ulcers healed

Study or Subgroup	Zinc sulphate Events	Zinc sulphate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Brewer 1967	5	6	4	7	100.0%	1.46 [0.70 , 3.04]
Total (95% CI)		**6**		**7**	**100.0%**	**1.46 [0.70 , 3.04]**
Total events:	5		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)
Test for subgroup differences: Not applicable

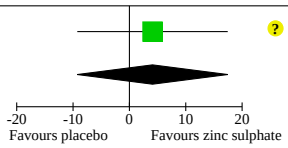


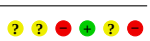
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 17.2. Comparison 17: Treatment: zinc sulphate versus placebo, Outcome 2: Change in pressure ulcer volume (mL)

Study or Subgroup	Zinc sulphate Mean [mL]	Zinc sulphate SD [mL]	Zinc sulphate Total	Placebo Mean [mL]	Placebo SD [mL]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [mL]
Norris 1971	10.1	9	10	6	17.5	8	100.0%	4.10 [-9.25 , 17.45]
Total (95% CI)			**10**			**8**	**100.0%**	**4.10 [-9.25 , 17.45]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable





Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

APPENDICES

Appendix 1. Cochrane Wounds Specialised Register

1 MESH DESCRIPTOR Pressure Ulcer EXPLODE ALL AND INREGISTER

2 pressure next (ulcer* or sore* or injur*) AND INREGISTER

3 decubitus next (ulcer* or sore*) AND INREGISTER

4 (bed next sore*) or bedsore* AND INREGISTER

5 #1 OR #2 OR #3 OR #4 AND INREGISTER

6 MESH DESCRIPTOR Nutritional Physiological Phenomena EXPLODE ALL AND INREGISTER

7 MESH DESCRIPTOR Nutrition Therapy EXPLODE ALL AND INREGISTER

8 MESH DESCRIPTOR Dietary Supplements EXPLODE ALL AND INREGISTER

9 MESH DESCRIPTOR Micronutrients EXPLODE ALL AND INREGISTER

10 MESH DESCRIPTOR dietary proteins EXPLODE ALL AND INREGISTER

11 MESH DESCRIPTOR Dietary Carbohydrates EXPLODE ALL AND INREGISTER

12 MESH DESCRIPTOR Dietary Fats EXPLODE ALL AND INREGISTER

13 MESH DESCRIPTOR Energy Intake EXPLODE ALL AND INREGISTER

14 nutrition* AND INREGISTER

15 diet* AND INREGISTER

16 tube next (fed or feed or feeding) AND INREGISTER

17 (nutrient* near3 (supplement* or fortification or capsule* or tablet* or liquid*)) AND INREGISTER

18 ((micronutrient* or micro-nutrient* or vitamin* or multivitamin* or mineral* or (trace next element*) or zinc or iodine or iron or cobalt or chromium or copper or manganese or fluoride or sodium or selenium or molybdenum) near3 (supplement* or fortification or capsule* or tablet* or liquid*)) AND INREGISTER

19 ((macronutrient* or macro-nutrient* or protein* or (amino next acid*) or carbohydrate* or calorie* or energ* or fat* or lipid*) near3 (supplement* or fortification or capsule* or tablet* or liquid* or intake)) AND INREGISTER

20 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 AND INREGISTER

21 #5 AND #20 AND INREGISTER

Appendix 2. The Cochrane Central Register of Controlled Clinical Trials (CENTRAL) via Cochrane Register of Studies

1 MESH DESCRIPTOR Pressure Ulcer EXPLODE ALL AND CENTRAL:TARGET

2 pressure next (ulcer* or sore* or injur*) AND CENTRAL:TARGET

3 decubitus next (ulcer* or sore*) AND CENTRAL:TARGET

4 (bed next sore*) or bedsore* AND CENTRAL:TARGET

5 #1 OR #2 OR #3 OR #4

6 MESH DESCRIPTOR Nutritional Physiological Phenomena EXPLODE ALL AND CENTRAL:TARGET

7 MESH DESCRIPTOR Nutrition Therapy EXPLODE ALL AND CENTRAL:TARGET

8 MESH DESCRIPTOR Dietary Supplements EXPLODE ALL AND CENTRAL:TARGET

9 MESH DESCRIPTOR Micronutrients EXPLODE ALL AND CENTRAL:TARGET

10 MESH DESCRIPTOR dietary proteins EXPLODE ALL AND CENTRAL:TARGET

11 MESH DESCRIPTOR Dietary Carbohydrates EXPLODE ALL AND CENTRAL:TARGET

12 MESH DESCRIPTOR Dietary Fats EXPLODE ALL AND CENTRAL:TARGET

13 MESH DESCRIPTOR Energy Intake EXPLODE ALL AND CENTRAL:TARGET

14 nutrition* AND CENTRAL:TARGET

15 diet* AND CENTRAL:TARGET

16 tube next (fed or feed or feeding) AND CENTRAL:TARGET

17 (nutrient* near3 (supplement* or fortification or capsule* or tablet* or liquid*)) AND CENTRAL:TARGET

18 ((micronutrient* or micro-nutrient* or vitamin* or multivitamin* or mineral* or (trace next element*) or zinc or iodine or iron or cobalt or chromium or copper or manganese or fluoride or sodium or selenium or molybdenum) near3 (supplement* or fortification or capsule* or tablet* or liquid*)) AND CENTRAL:TARGET

19 ((macronutrient* or macro-nutrient* or protein* or (amino next acid*) or carbohydrate* or calorie* or energ* or fat* or lipid*) near3 (supplement* or fortification or capsule* or tablet* or liquid* or intake)) AND CENTRAL:TARGET

20 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

21 #5 AND #20

Trial registry specific search appended to above strategy - Cochrane Central Register of Controlled Clinical Trials (CENTRAL) via Cochrane Register of Studies

22 (NCT0* or ACTRN* or ChiCTR* or DRKS* or EUCTR* or eudract* or IRCT* or ISRCTN* or JapicCTI* or JPRN* or NTR0* or NTR1* or NTR2* or NTR3* or NTR4* or NTR5* or NTR6* or NTR7* or NTR8* or NTR9* or SRCTN* or UMIN0*):AU AND CENTRAL:TARGET 335781

23 http*:SO AND CENTRAL:TARGET

24 #22 OR #23

25 #21 AND #24

Appendix 3. MEDLINE Ovid

1 exp Pressure ulcer/

2 (pressure adj (ulcer* or sore* or injur*)).ti,ab.

3 (decubitus adj (ulcer* or sore*)).ti,ab.

4 (bedsore* or (bed adj sore*)).ti,ab.

5 or/1-4

6 exp Nutritional Physiological Phenomena/

7 exp Nutrition Therapy/

8 exp Dietary Supplements/

9 exp Micronutrients/

10 exp Dietary Proteins/

11 exp Dietary Carbohydrates/

12 exp Dietary Fats/

13 exp Energy Intake/

14 nutrition*.ti,ab.

15 diet*.ti,ab.

16 (nutrient* adj3 (supplement* or fortification or capsule* or tablet* or liquid*)).ti,ab.

17 ((micronutrient* or micro-nutrient* or vitamin* or multivitamin* or mineral* or trace next element* or zinc or iodine or iron or cobalt or chromium or copper or manganese or fluoride or sodium or selenium or molybdenum) adj3 (supplement* or fortification or capsule* or tablet* or liquid*)).ti,ab.

18 ((macronutrient* or macro-nutrient* or protein* or amino next acid* or carbohydrate* or calorie* or energ* or fat* or lipid*) adj3 (supplement* or fortification or capsule* or tablet* or liquid* or intake)).ti,ab.

19 (tube adj (fed or feed or feeding)).ti,ab.

20 or/6-19

21 5 and 20

22 randomized controlled trial.pt.

23 controlled clinical trial.pt.

24 randomized.ab.

25 placebo.ab.

26 drug therapy.fs.

27 randomly.ab.

28 trial.ab.

29 groups.ab.

30 or/22-29

31 exp animals/ not humans.sh.

32 30 not 31

33 21 and 32

Appendix 4. Embase Ovid

1 exp Decubitus/

2 (pressure adj (ulcer* or sore* or injur*)).ti,ab.

3 (decubitus adj (ulcer* or sore*)).ti,ab.

4 (bedsore* or (bed adj sore*)).ti,ab.

5 or/1-4

6 exp Nutrition/

7 exp diet therapy/

8 exp Dietary Supplements/

9 exp Micronutrients/

10 exp Dietary Proteins/

11 exp Dietary Carbohydrates/

12 exp Dietary Fats/

13 exp Energy Intake/

14 nutrition*.ti,ab.

15 diet*.ti,ab.

16 (nutrient* adj3 (supplement* or fortification or capsule* or tablet* or liquid*)).ti,ab.

17 ((micronutrient* or micro-nutrient* or vitamin* or multivitamin* or mineral* or trace next element* or zinc or iodine or iron or cobalt or chromium or copper or manganese or fluoride or sodium or selenium or molybdenum) adj3 (supplement* or fortification or capsule* or tablet* or liquid*)).ti,ab.

18 ((macronutrient* or macro-nutrient* or protein* or amino next acid* or carbohydrate* or calorie* or energ* or fat* or lipid*) adj3 (supplement* or fortification or capsule* or tablet* or liquid* or intake)).ti,ab.

19 (tube adj (fed or feed or feeding)).ti,ab.

20 or/6-19

21 5 and 20

22 Randomized controlled trial/

23 Controlled clinical study/

24 Random$.ti,ab.

25 randomization/

26 intermethod comparison/

27 placebo.ti,ab.

28 (compare or compared or comparison).ti.

29 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.

30 (open adj label).ti,ab.

31 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

32 double blind procedure/

33 parallel group$1.ti,ab.

34 (crossover or cross over).ti,ab.

35 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 orintervention$1 or patient$1 or subject$1 or participant $1)).ti,ab.

36 (assigned or allocated).ti,ab.

37 (controlled adj7 (study or design or trial)).ti,ab.

38 (volunteer or volunteers).ti,ab.

39 human experiment/

40 trial.ti.

41 or/22-40

42 (random$ adj sampl$ adj7 (cross section$ or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)

43 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)

44 (((case adj control$) and random$) not randomi?ed controlled).ti,ab.

45 (Systematic review not (trial or study)).ti.

46 (nonrandom$ not random$).ti,ab.

47 Random field$.ti,ab.

48 (random cluster adj3 sampl$).ti,ab.

49 (review.ab. and review.pt.) not trial.ti.

50 we searched.ab. and (review.ti. or review.pt.)

51 update review.ab.

52 (databases adj4 searched).ab.

53 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/

54 Animal experiment/ not (human experiment/ or human/)

55 or/42-54

56 41 not 55

57 21 and 56

Appendix 5. CINAHL Plus EBSCO

S51 S27 AND S50

S50 S49 NOT S48

S49 S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42

S48 S46 NOT S47

S47 MH (human)

S46 S43 OR S44 OR S45

S45 TI (animal model*)

S44 MH (animal studies)

S43 MH animals+

S42 AB (CLUSTER W3 RCT)

S41 MH (crossover design) OR MH (comparative studies)

S40 AB (control W5 group)

S39 PT (randomized controlled trial)

S38 MH (placebos)

S37 MH (sample size) AND AB (assigned OR allocated OR control)

S36 TI (trial)

S35 AB (random*)

S34 TI (randomised OR randomized)

S33 MH cluster sample

S32 MH pretest-posttest design

S31 MH random assignment

S30 MH single-blind studies

S29 MH double-blind studies

S28 MH randomized controlled trials

S27 S5 AND S26

S26 S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25

S25 TI ((tube N1 (fed or feed or feeding))) OR AB ((tube N1 (fed or feed or feeding)))

S24 TI (((macronutrient* or macro-nutrient* or protein* or amino next acid* or carbohydrate* or calorie* or energ* or fat* or lipid*) N3 (supplement* or fortification or capsule* or tablet* or liquid* or intake))) OR AB (((macronutrient* or macro-nutrient* or protein* or amino next acid* or carbohydrate* or calorie* or energ* or fat* or lipid*) N3 (supplement* or fortification or capsule* or tablet* or liquid* or intake)))

S23 TI (((micronutrient* or micro-nutrient* or vitamin* or multivitamin* or mineral* or trace next element* or zinc or iodine or iron or cobalt or chromium or copper or manganese or fluoride or sodium or selenium or molybdenum) N3 (supplement* or fortification or capsule* or tablet* or liquid*))) OR AB (((micronutrient* or micro-nutrient* or vitamin* or multivitamin* or mineral* or trace next element* or zinc or iodine or iron or cobalt or chromium or copper or manganese or fluoride or sodium or selenium or molybdenum) N3 (supplement* or fortification or capsule* or tablet* or liquid*)))

S22 TI ((nutrient* N3 (supplement* or fortification or capsule* or tablet* or liquid*))) OR AB ((nutrient* N3 (supplement* or fortification or capsule* or tablet* or liquid*)))

S21 TI diet* OR AB diet*

S20 TI nutrition* OR AB nutrition*

S19 (MH "Energy Intake")

S18 (MH "Trace Elements+")

S17 (MH "Minerals+")

S16 (MH "Vitamins+")

S15 (MH "Nutrients+")

S14 (MH "Dietary Carbohydrates+")

S13 (MH "Dietary Fats+")

S12 (MH "Dietary Proteins+")

S11 (MH "Dietary Supplements+")

S10 (MH "Diet Therapy+")

S9 (MH "Diet+")

S8 (MH "Nutritional Support+")

S7 (MH "Nutritional Physiology+")

S6 (MH "Nutrition+")

S5 S1 OR S2 OR S3 OR S4

S4 TI ((bedsore* or (bed N1 sore*))) OR AB ((bedsore* or (bed N1 sore*)))

S3 TI ((decubitus N1 (ulcer* or sore*))) OR AB ((decubitus N1 (ulcer* or sore*)))

S2 TI ((pressure N1 (ulcer* or sore* or injur*))) OR AB ((pressure N1 (ulcer* or sore* or injur*)))

S1 (MH "Pressure Ulcer+")

Appendix 6. US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov)

nutrition OR diet OR enteral OR parenteral OR feed OR food OR supplement | Pressure Ulcer

nutrition OR diet OR enteral OR parenteral OR feed OR food OR supplement | Pressure Injury

nutrition OR diet OR enteral OR parenteral OR feed OR food OR supplement | Decubitus

nutrition OR diet OR enteral OR parenteral OR feed OR food OR supplement | Bedsore

Appendix 7. World Health Organization International Clinical Trials Registry Platform

nutrition OR diet OR enteral OR parenteral OR feed OR food OR supplement | Pressure Ulcer

nutrition OR diet OR enteral OR parenteral OR feed OR food OR supplement | Pressure Injury

nutrition OR diet OR enteral OR parenteral OR feed OR food OR supplement | Decubitus

nutrition OR diet OR enteral OR parenteral OR feed OR food OR supplement | Bedsore

Appendix 8. Search strategy for the original published version

The Cochrane Wounds Group Specialised Trials Register was searched for reports of trials evaluating nutritional interventions in the prevention and treatment of pressure ulcers in September 2002. The Trials Register has been developed and maintained by regular searches, using a maximally sensitive search strategy for retrieving randomised controlled trials, of 19 electronic databases, as well as handsearching of wound care journals and conference proceedings, and is regularly updated.

The Cochrane Central Register of Controlled Trials (CENTRAL) was also searched (Issue 3, 2002) using the following strategy:
1. (decubitus next ulcer*)
2. (bed and sore*)
3. (pressure and sore*)
4. (pressure and ulcer*)
5. DECUBITUS-ULCER*:ME
6. ((((#1 or #2) or #3) or #4) or #5)
7. nutrition*
8. diet*
9. tube-fe*
10. NUTRITION*:ME
11. DIET*:ME
12. DIET-THERAPY*:ME
13. NUTRITIONAL-SUPPORT*:ME
14. ENTERAL-NUTRITION*:ME
15. PARENTERAL-NUTRITION*:ME
16. (((((((#7 or #8) or #9) or #10) or #11) or #12) or #13) or #14) or #15)
17. (#6 and #16)

MEDLINE was searched in June 2003 via PubMed using the following strategy:
1. (bed sore) OR bedsore OR (pressure sore) OR (decubitus ulcer) OR (pressure ulcer) OR (decubital ulcer) OR (ischaemic ulcer)
2. "Decubitus Ulcer"[MESH]
3. nutri* OR diet OR food
4. "nutrition"[MESH] OR "Diet"[MESH] OR "Food"[MESH] OR "Nutritional Support"[MESH]
5. enteral OR parenteral OR proteins OR vitamins OR minerals
6. "Amino Acids, Peptides, and Proteins"[MESH] OR "Dietary Supplements"[MESH] OR "Growth Substances, Pigments, and Vitamins"[MESH] OR "Enzymes, Coenzymes, and Enzyme Inhibitors"[MESH] OR "Lipids and Antilipaemic Agents"[MESH] OR "Minerals"[MESH]
7. therapy OR prophylaxis OR prevention
8. (randomized controlled trial[PTYP] OR drug therapy[SH] OR therapeutic use[SH:NOEXP] OR random*[WORD])
9. systematic[sb]
10. (cohort studies[MESH] OR risk[MESH] OR (odds[WORD] AND ratio*[WORD]) OR (relative[WORD] AND risk[WORD]) OR (case control*[WORD] OR case-control studies[MESH]))
11. (incidence[MESH] OR mortality[MESH] OR follow-up studies[MESH] OR mortality[SH] OR prognos*[WORD] OR predict*[WORD] OR course[WORD])
12. (#1 OR #2) AND (#3 OR #4 OR #5 OR #6) AND (#7 OR #8 OR #9 OR #10 OR #11)

CINAHL was searched via Ovid in June 2003 with the following query:
1. exp Pressure ulcer/nu, dh, pc, et, rf, th, me [Nursing, Diet Therapy, Prevention and Control, Etiology, Risk Factors, Therapy, Metabolism]
2. PARENTERAL NUTRITION SOLUTIONS/ or ENTERAL NUTRITION/ or TOTAL PARENTERAL NUTRITION/ or PERIPHERAL PARENTERAL NUTRITION/ or PARENTERAL NUTRITION/ or NUTRITION/
3. 1 and 2

The listed databases were searched by the authors for eligible studies for the earliest entrance date possible until the latest search date. For this review, there were no restrictions regarding date of publication, language of publication, or publication status (published or unpublished work). Experts in the field, such as scientific societies for wound healing and treatment, for nutrition and for nutritional medicine, were contacted and asked whether they had been involved in any further studies or were aware of recent or ongoing studies on the effect of nutrition in the prevention and treatment of pressure ulcers.

We handsearched the following conference proceedings to identify any research or relevant studies:

- the Congress of the European Society of Parenteral and Enteral Nutrition (ESPEN) 1996 -2002
- the Meetings of the European Pressure Ulcer Advisory Panel (EPUAP) 1997 - 2000

Some additional journals to those stated in the protocol were considered suitable for handsearching. The following journals were searched by hand from 1996 to 2002:

- Advances in Wound Care,
- Advances in Food and Nutrition Research,
- Clinical Nutrition,
- European Journal of Clinical Nutrition,
- European Journal of Nutrition,
- Wundforum,
- Zeitschrift fuer Wundbehandlung,
- Zeitschrift fuer Wundheilung,
- Zeitschrift fuer Gerontologie und Geriatrie,
- Aktuelle Ernaehrungsmedizin,
- Deutsches Wundjournal

Studies and articles cited in articles identified have also been checked for eligibility.

We tried to identify unpublished studies by contacting manufacturers of nutritional supplements (Fresenius, NutriScience, Pfrimmer, Braun, Ratiopharm, Aventis and Novartis), but this yielded no further studies.

Appendix 9. Summary of findings 7: protein, arginine, zinc and antioxidants compared to placebo for the prevention of pressure ulcers

Summary of findings

Protein, arginine, zinc and antioxidants compared to placebo for the prevention of pressure ulcers

Patient or population: patients with a hip fracture

Setting: hospital (3 centres treating people with hip fractures), The Netherlands

Intervention: protein, arginine, zinc and antioxidants

Comparison: placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with protein, arginine, zinc and antioxidants**				
Incidence of pressure ulcers follow-up: 4 weeks	577 per 1000	**531 per 1000** (375 to 750)	**RR 0.92** (0.65 to 1.30)	103 (1 RCT)	⊕◯◯◯ Very low[a]	

(Continued)

Time to pressure ulcer development - not reported	-	-	-	-	-
Acceptability of nutritional supplements - not reported	-	-	-	-	-
Side effects - not reported	-	-	-	-	-
Costs - not reported	-	-	-	-	-
Health-related quality of life - not reported	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[Enter text here]

Appendix 10. Summary of findings 8: L-carnitine, L-leucine, calcium, magnesium and vitamin D compared to standard diet for the prevention of pressure ulcers

Summary of findings:

L-carnitine, L-leucine, calcium, magnesium and vitamin D compared to standard diet for the prevention of pressure ulcers

Patient or population: patients (age > 65 years) with diagnosis of proximal fracture of the pelvis due to an accidential fall

Setting: hospital (Italy)

Intervention: L-carnitine, L-leucine, calcium, magnesium and vitamin D

Comparison: standard diet

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard diet	**Risk with L-carnitine, L-leucine, calcium, magnesium and vitamin D**				
Incidence of pressure ulcers follow-up: 6 weeks	146 per 1000	**79 per 1000** (22 to 294)	**RR 0.54**	79 (1 RCT)	⨁◯◯◯ Very low[a,b]	

(Continued)

			(0.15 to 2.01)		
Time to pressure ulcer development - not reported	-	-	-	-	-
Acceptability of nutritional supplements - not reported	-	-	-	-	-
Side effects - not reported	-	-	-	-	-
Costs - not reported	-	-	-	-	-
Health-related quality of life - not reported	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Appendix 11. Summary of findings 9: EPA, GLA and antioxidants compared to standard diet for the prevention of pressure ulcers

Summary of findings:

EPA, GLA and antioxidants compared to standard diet for the prevention of pressure ulcers

Patient or population: patients suffering from acute lung injury

Setting: hospital, intensive care unit (Israel)

Intervention: EPA, GLA and antioxidants

Comparison: standard diet

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard diet	**Risk with EPA, GLA and antioxidants**				
Incidence of pressure ulcers follow-up: 1 weeks	20 per 1000	**65 per 1000** (7 to 605)	**RR 3.20** (0.34 to 29.63)	95 (1 RCT)	⊕◯◯◯ Very low[a,b]	

(Continued)

Time to pressure ulcer development - not reported	-	-	-	-	-
Acceptability of nutritional supplements - not reported	-	-	-	-	-
Side effects - not reported	-	-	-	-	-
Costs - not reported	-	-	-	-	-
Health-related quality of life - not reported	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Appendix 12. Summary of findings 10: Disease-specific supplement (reduced carbohydrate, modified fat) compared to standard high-carbohydrate formula for the prevention of pressure ulcers

Summary of findings: 6

Disease-specific supplement (reduced carbohydrate, modified fat) compared to standard high-carbohydrate formula for the prevention of pressure ulcers

Patient or population: patients ≥ 50 years old with a history of type 2 diabetes mellitus or documented hyperglycaemia who required total enteral nutrition support by tube

Setting: long-term care facilities (USA)

Intervention: a disease-specific supplement with reduced carbohydrate and modified-fat formula

Comparison: a standard high-carbohydrate formula

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with a standard high-carbohydrate formula	**Risk with a disease-specific supplement with reduced carbohydrate and modified-fat formula**				
Incidence of pressure ulcers	538 per 1000	**431 per 1000**	**RR 0.80**	27	⊕◯◯◯	

(Continued) follow-up: 12 weeks		(194 to 942)	(0.36 to 1.75)	(1 RCT)	Very low[a,b]
Time to pressure ulcer development - not reported	-	-	-	-	-
Acceptability of nutritional supplements - not reported	-	-	-	-	-
Side effects - not reported	-	-	-	-	-
Costs - not reported	-	-	-	-	-
Health-related quality of life - not reported	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Appendix 13. Summary of findings 11: Different doses of arginine for treating pressure ulcers

Summary of findings:

Different doses of arginine for treating pressure ulcers

Patient or population: patients with pressure ulcers

Setting: hospital in Australia

Intervention: 9 g arginine

Comparison: 4.5 g arginine

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 4.5 g arginine	**Risk with 9 g arginine**				
Pressure ulcers healed - not reported	-	-	-	-	-	
Time to complete healing of pressure ulcers - not reported	-	-	-	-	-	

(Continued)

Change in area/depth/volume of pressure ulcers - not reported	-	-	-	-	-
Acceptability of nutritional supplements: non-adherence follow-up: 3 weeks	83 per 1000	**91 per 1000** (7 to 1000)	**RR 1.09** (0.08 to 15.41)	23 (1 RCT)	⊕◯◯◯ Very low[a,b]
At least one side effect follow-up: 3 weeks	0 per 1000	**0 per 1000** (0 to 0)	**RR 2.81** (0.12 to 63.83)	29 (1 RCT)	⊕◯◯◯ Very low[a,b]
Costs - not reported	-	-	-	-	-
Health-related quality of life - not reported	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Appendix 14. Summary of findings 12: EPA, GLA and antioxidants compared to standard diet for treating pressure ulcers

Summary of findings:

EPA, GLA and antioxidants compared to standard diet for treating pressure ulcers

Patient or population: patients with pressure ulcers suffering from acute lung injury

Setting: intensive care unit of a hospital in Israel

Intervention: EPA, GLA and antioxidants

Comparison: standard diet

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard diet	**Risk with EPA, GLA and antioxidants**				
Pressure ulcers healed follow-up: 1 weeks	0 per 1000	**0 per 1000** (0 to 0)	Not estimable	95 (1 RCT)	⊕◯◯◯ Very low[a,b]	No number of events

(Continued)

Time to complete healing of pressure ulcers - not reported	-	-	-	-	-
Change in area/depth/volume of pressure ulcers - not reported	-	-	-	-	-
Acceptability of nutritional supplements - not reported	-	-	-	-	-
Side effects - not reported	-	-	-	-	-
Costs - not reported	-	-	-	-	-
Health-related quality of life - not reported	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Appendix 15. Summary of findings 13: Protein compared to standard diet for treating pressure ulcers

Summary of findings:

Protein compared to standard diet for treating pressure ulcers

Patient or population: tube-fed patients with pressure ulcers; patients > 70 years with malnutrition and pressure ulcers

Setting: medical centre in the USA, and nursing home in France

Intervention: protein

Comparison: standard diet

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard diet	**Risk with protein**				
Pressure ulcers healed follow-up: 8 weeks	0 per 1000	**0 per 1000** (0 to 0)	**RR 9.00** (0.59 to 137.65)	12 (1 RCT)	⊕◯◯◯ Very low[a,b]	

(Continued)

Pressure ulcer episodes follow-up: 6 weeks	69 per 1000	**80 per 1000** (26 to 240)	**RR 1.15** (0.38 to 3.46)	160 (1 RCT)	⊕◯◯◯ Very low[c,d]
Time to complete healing of pressure ulcers - not reported	-	-	-	-	-
Change in area/depth/volume of pressure ulcers - not reported	-	-	-	-	-
Acceptability of nutritional supplements - not reported	-	-	-	-	-
Side effects: diarrhoea episodes follow-up: 6 weeks	83 per 1000	**12 per 1000** (2 to 102)	**RR 0.15** (0.02 to 1.22)	152 (1 RCT)	⊕◯◯◯ Very low[e,f]
Costs (EUR) follow-up: 6 weeks	The mean costs (EUR) was **1076**	MD **191 lower** (240.63 lower to 141.37 lower)	-	175 (1 RCT)	⊕⊕◯◯ Low[e,g]
Health-related quality of life - not reported	-	-	-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Appendix 16. Summary of findings 14: Specialised amino acid mixture (arginine-enriched) compared to standard diet for treating pressure ulcers

Summary of findings:

Specialised amino acid mixture (arginine-enriched) compared to standard diet for treating pressure ulcers

Patient or population: adults with at least one pressure ulcer

Setting: hospital in China

Intervention: a specialised amino acid mixture (arginine-enriched)

Comparison: standard diet or placebo

(Continued)

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard diet or placebo	**Risk with a specialised amino acid mixture (arginine-enriched)**				
Pressure ulcers healed - not reported	-	-	-	-	-	
Time to complete healing of pressure ulcers - not reported	-	-	-	-	-	
Change in area/depth/volume of pressure ulcers - not reported	-	-	-	-	-	
Acceptability of nutritional supplements - not reported	-	-	-	-	-	
Side effects: at least one adverse gastrointestinal event follow-up: 4 weeks	0 per 1000	**0 per 1000** (0 to 0)	Not estimable	87 (1 RCT)	⨁⨁◯◯ Low[a,b]	No number of events
Costs - not reported	-	-	-	-	-	
Health-related quality of life - not reported	-	-	-	-	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Appendix 17. Summary of findings 15: Ornithine alpha-ketoglutarate compared to placebo for treating pressure ulcers

Summary of findings:

Ornithine alpha-ketoglutarate compared to placebo for treating pressure ulcers

Patient or population: people > 60 years with heel pressure ulcers (NPUAP stage 2 or 3) occurring after accidental immobilization, ulcer in the process of recovery with early signs of granulation tissue

(Continued)

Setting: hospitals in Bulgaria, France, Germany, Italy, Romania, and Spain (67 wards: geriatric, internal medicine, physical medicine and rehabilitation, trauma, plastic surgery, cardiology, neurology and dermatology), in- and outpatient settings

Intervention: Ornithine alpha-ketoglutarate

Comparison: placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with Ornithine alpha-ketoglutarate**				
Pressure ulcers healed - not reported	-	-	-	-	-	
Time to complete healing of pressure ulcers - not reported	-	-	-	-	-	
Change in pressure ulcer area (cm^2) follow-up: 6 weeks	The mean change in pressure ulcer area (cm^2) was **-1.7** cm^2	MD **0.6 cm^2 lower** (1.9 lower to 0.7 higher)	-	93 (1 RCT)	⨁◯◯◯ Very low[a,b]	Several measures (cm^2 and percentage) of the same outcome (change in pressure ulcer area) due to different studies.
Change in pressure ulcer area (percentage) follow-up: 6 weeks	The mean change in pressure ulcer area (percentage) was **-54** %	MD **5.5 % lower** (34.04 lower to 23.04 higher)	-	93 (1 RCT)	⨁◯◯◯ Very low[a,c]	
Acceptability of nutritional supplements - not reported	-	-	-	-	-	
Side effects follow-up: 6 weeks	160 per 1000	**176 per 1000** (88 to 352)	**RR 1.10** (0.55 to 2.20)	160 (1 RCT)	⨁◯◯◯ Very low[a,d]	
Costs - not reported	-	-	-	-	-	
Health-related quality of life - not reported	-	-	-	-	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence

(Continued)

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Appendix 18. Summary of findings 16: Vitamin C compared to placebo for treating pressure ulcers

Summary of findings:

Vitamin C compared to placebo for treating pressure ulcers

Patient or population: surgical and other patients with pressure ulcers

Setting: university hospital in UK, and nursing homes (n = 11) and hospital (n = 1) in The Netherlands

Intervention: vitamin C

Comparison: placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with vitamin C**				
Pressure ulcers healed follow-up: 12 weeks	455 per 1000	**505 per 1000** (218 to 1000)	**RR 1.11** (0.48 to 2.60)	108 (2 RCTs)	⊕◯◯◯ Very low[a,b]	
Time to complete healing of pressure ulcers - not reported	-	-	-	-	-	
Change in pressure ulcer area (percentage) follow-up: 12 weeks	The mean change in pressure ulcer area (percentage) was **-42.7** %	MD **41.3 % lower** (62.1 lower to 20.5 lower)	-	20 (1 RCT)	⊕◯◯◯ Very low[c,d]	
Acceptability of nutritional supplements - not reported	-	-	-	-	-	
Side effects - not reported	-	-	-	-	-	
Costs - not reported	-	-	-	-	-	
Health-related quality of life - not reported	-	-	-	-	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

(Continued)

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Appendix 19. Summary of findings 17: Zinc sulphate compared to placebo for treating pressure ulcers

Summary of findings:

Zinc sulphate compared to placebo for treating pressure ulcers

Patient or population: spinal cord injury patients with poorly healing pressure ulcers and patients with pressure ulcers

Setting: hospital in the USA, and unclear setting

Intervention: zinc sulphate

Comparison: placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with zinc sulphate**				
Pressure ulcers healed follow-up: 1 follow-up not reported	571 per 1000	**834 per 1000** (400 to 1000)	**RR 1.46** (0.70 to 3.04)	13 (1 RCT)	⊕◯◯◯ Very low[a,b]	
Time to complete healing of pressure ulcers - not reported	-	-	-	-	-	
Change in pressure ulcer volume (mL) follow-up: 12 weeks	The mean change in pressure ulcer volume (mL) was **6** mL	MD **4.1 mL higher** (9.25 lower to 17.45 higher)	-	18 (1 RCT)	⊕◯◯◯ Very low[c,d]	
Acceptability of nutritional supplements - not reported	-	-	-	-	-	
Side effects - not reported	-	-	-	-	-	
Costs - not reported	-	-	-	-	-	
Health-related quality of life - not reported	-	-	-	-	-	

(Continued)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

WHAT'S NEW

Date	Event	Description
12 February 2024	New citation required but conclusions have not changed	New search, switched to RoB 2 and GRADEproGDT, 33 studies included in total
12 February 2024	New search has been performed	Third update with new search.

HISTORY

Protocol first published: Issue 4, 2002
Review first published: Issue 4, 2003

Date	Event	Description
25 March 2014	New citation required and conclusions have changed	First update, new search, 15 additional trials included bringing the total to 23 trials.
25 March 2014	New search has been performed	Three review authors left the team and did not contribute to this update (G. Schloemer, O. Kuss, J. Behrens)
15 April 2008	Amended	Converted to new review format.
21 August 2003	New citation required and conclusions have changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

Gero Langer examined bibliographies, assessed the studies, entered the data, conducted data analyses, worked on the summary of findings tables, edited the review and co-ordinated the review update.

Ching Shan Wan examined bibliographies, assessed the studies, entered the data, conducted data analyses and edited the review.

Daniela Schoberer examined bibliographies, assessed the studies, entered the data, conducted data analyses and edited the review.

Lukas Schwingshackl worked on the summary of findings tables.

Astrid Fink examined bibliographies, assessed the studies, entered the data, conducted data analyses and edited the review.

DECLARATIONS OF INTEREST

G Langer: no conflict of interest
CS Wan: no conflict of interest
D Schoberer: no conflict of interest
L Schwingshackl: no conflict of interest
A Fink: no conflict of interest

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Internal sources

- Authors were supported by their institutions, Other

  None

External sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between the last version of the review, published in 2014 and the current update

We updated our search terms by adding new pressure injury terms and added relevant intervention MESH terms and keywords.

We have extended the primary outcome: In former versions, the primary outcome for treatment studies was only time to complete healing, but as other outcomes are clinically important, too, we extended the primary outcome to time to complete healing, pressure ulcers healed, and size and depth of pressure ulcers (for treatment studies).

Furthermore, we decided to exclude studies in which pressure ulcers were only a side effect and in which it was moreover not clear whether pressure ulcers already existed baseline. In these studies, neither the incidence of new pressure ulcers nor the progression of pressure ulcers can be determined. This was not specified in the former version or the protocol. As a result of this specification, one study from the former review was excluded in this review version.

We have more clearly defined the intervention: In the former version and the protocol we did not mention how we deal with multifactorial interventions, where one component is a nutrition intervention. We decided to exclude these studies because the effect of the nutritional supplement cannot be inferred from these studies. Accordingly, a study that was included in the former review was excluded in this review.

We did not perform the planned subgroup analyses (setting-specific, patient characteristics specific, mode of feeding specific). The included trials were heterogenous with regard to participants, and to nutritional interventions and comparable nutritional supplements were only examined by a few studies. In addition, the supplements were administered enterally in all studies.

There were insufficient studies and data to perform the planned sensitivity analysis. We had a maximum of 4 studies in meta-analysis and only one outcome of a single study without concerns in the risk of bias assessment. These analyses were not reported (too much strain on the data).

We have changed the assessment of bias risk to the Risk of Bias 2 (RoB2) tool.

We have implemented GRADE by using GRADEpro GDT in this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Dietary Proteins [administration & dosage]; *Dietary Supplements; *Pressure Ulcer [diet therapy] [prevention & control]; Quality of Life; Randomized Controlled Trials as Topic; *Wound Healing

MeSH check words

Humans