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Oral calorie supplements for cystic fibrosis (Review)

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[Intervention Review]

Oral calorie supplements for cystic fibrosis

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ABSTRACT

Background

Poor nutrition occurs frequently in people with cystic fibrosis and is associated with other adverse outcomes. Oral calorie supplements are used to increase total daily calorie intake and improve weight gain. However, they are expensive and there are concerns they may reduce the amount of food eaten and not improve overall energy intake. This is an update of a previously published review.

Objectives

To establish whether in people with cystic fibrosis, oral calorie supplements: increase daily calorie intake; and improve overall nutritional intake, nutritional indices, lung function, survival and quality of life. To assess adverse effects associated with using these supplements.

Search methods

We searched the Cochrane Cystic Fibrosis Trials Register comprising references from comprehensive electronic database searches, handsearches of relevant journals and abstract books of conference proceedings. We contacted companies marketing oral calorie supplements.

Last search: 18 October 2016.

Selection criteria

Randomised or quasi-randomised controlled trials comparing use of oral calorie supplements for at least one month to increase calorie intake with no specific intervention or additional nutritional advice in people with cystic fibrosis.

Data collection and analysis

We independently selected the included trials, assessed risk of bias and extracted data. We contacted the authors of included trials and obtained additional information for two trials.

Main results

We identified 21 trials and included three, reporting results from 131 participants lasting between three months and one year. Two trials compared supplements to additional nutritional advice and one to no intervention. Two of the included trials recruited only children. In one trial the risk of bias was low across all domains, in a second trial the risk of bias was largely unclear and in the third mainly low. Blinding of participants was unclear in two of the trials. Also, in one trial the clinical condition of groups appeared to be unevenly balanced at baseline and in another trial there were concerns surrounding allocation concealment. There were no significant differences between people receiving supplements or dietary advice alone for change in weight, height, body mass index, z score or other indices of nutrition or growth. Changes in weight (kg) at three, six and 12 months respectively were: mean difference (MD) 0.32 (95% confidence interval (CI) -0.09 to 0.72); MD 0.47 (95% CI -0.07 to 1.02); and MD 0.16 (-0.68 to 1.00). Total calorie intake was greater in people taking supplements at

12 months, MD 265.70 (95% CI 42.94 to 488.46). There were no significant differences between the groups for anthropometric measures of body composition, lung function, gastro-intestinal adverse effects or activity levels. Moderate quality evidence exists for the outcomes of changes in weight and height and low quality evidence exists for the outcomes of change in total calories, total fat and total protein intake as results are applicable only to children between the ages of 2 and 15 years and many post-treatment diet diaries were not returned. Evidence for the rate of adverse events in the treatment groups was extremely limited and judged to be of very low quality

Authors' conclusions

Oral calorie supplements do not confer any additional benefit in the nutritional management of moderately malnourished children with cystic fibrosis over and above the use of dietary advice and monitoring alone. While nutritional supplements may be used, they should not be regarded as essential. Further randomised controlled trials are needed to establish the role of short-term oral protein energy supplements in people with cystic fibrosis and acute weight loss and also for the long-term nutritional management of adults with cystic fibrosis or advanced lung disease, or both.

PLAIN LANGUAGE SUMMARY

Use of oral supplements to increase calorie intake in people with cystic fibrosis

We reviewed the evidence for the use of oral supplements to increase calorie intake in people with cystic fibrosis.

Background

Cystic fibrosis affects many organs, including the digestive system, and can lead to food not being absorbed as it should be, which in turn leads to growth problems. Children with cystic fibrosis need more energy than other children, but they often have reduced appetites. Poor diet has been linked to poor outcomes in cystic fibrosis. Milks or juices containing additional calories are often added to the diets of children with cystic fibrosis to increase their total daily calorie intake and help them gain weight. However, these supplements are expensive and may not achieve the desired effect if patients take them as a substitute for calories consumed from food rather than as an additional component. In toddlers or young children use of supplements may risk compromising the development of normal eating behaviour. This is an updated version of the review.

Search date

We last searched for evidence on 18 October 2016.

Study characteristics

This review includes three randomised controlled trials with a total of 131 participants and two of them only included children. Two of the trials compared supplements to dietary advice and one compared supplements to no advice. The trials lasted between three months and one year.

Key results

There were no major differences between people receiving supplements or just dietary advice for any nutritional or growth measurements. This was also true for measures of body composition, lung function, adverse effects on the digestive system or people's levels of activity. Advice and monitoring appear to be enough to manage the diet of moderately malnourished children.

Future trials should look into the use of calorie supplements for acute weight loss or long-term care for adults with cystic fibrosis.

Quality of the evidence

One of the trials appeared to be well run and the risk of bias was low for all the aspects of trial design that we assessed; so we do not think any bias will influence the results in a negative way. In the other two trials, we were not sure if the people taking part could guess which treatment group they were in. In one of these two trials, we further thought it was likely that the person recruiting them to the trial knew which group the participant would be in. In the second of these trials, the people in the group receiving supplements appeared to be generally in better clinical condition at the start of the trial than those who didn't receive any supplements or advice. These factors affect our confidence in the results from these trials.

We judged the quality of the evidence for the changes in weight and height to be moderate, but judged the quality of the evidence for the changes in total calories, total fat and total protein intake as low since results are applicable only to children aged between 2 and 15 years; also many post-treatment diet diaries were not returned to the investigators. Evidence for the rate of adverse events in the treatment groups was extremely limited and judged to be of very low quality.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings

Oral calorie supplements compared with control for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: oral calorie supplements

Comparison: control (no intervention, dietary advice or nutritional counselling)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control (no intervention, dietary advice or nutritional counselling)	Oral calorie supplements				
Change in weight (kg):[1] at 12 months Follow-up: up to 12 months	The mean change in weight was 2.97 kg gained in the control group.	The mean change in weight was 0.16 kg extra gained (0.68 kg lost to 1.00 kg extra gained) in the treatment group.	NA	102 (1 trial)	⊕⊕⊕⊖ **moderate**[2]	There was also no significant difference between treatment groups at 3 months (MD 0.32 kg, 95% CI -0.09 kg to 0.72 kg, 112 participants, 2 trials) or at 6 months (MD 0.47 kg, 95% CI -0.07 kg to 1.02 kg, 117 participants, 2 trials). There was also no significant difference in change in weight centile between treatment groups at 3, 6 and 12 months.
Change in height (cm):[1] at 12 months Follow-up: up to 12 months	The mean change in height was 5.85 cm gained in the control group.	The mean change in height was 0.06 cm extra gained (0.50 cm lost to 0.62 cm extra gained) in the treatment group.	NA	102 (1 trial)	⊕⊕⊕⊖ **moderate**[2]	There was also no significant difference between treatment groups at 3 months (MD -0.04 cm, 95% CI -0.36 cm to 0.29 cm, 112 participants, 2 trials) or at 6 months (MD -0.47 cm, 95% CI -1.32 cm to 0.38 cm, 101 participants, 1 trial). There was also no significant difference in change in height centile between treatment groups at 3, 6 and 12 months.

Change in total calories (Kcal/day): at 12 months Follow-up: up to 12 months	The mean change in total calories was 139.52 Kcal/day in the control group.	The mean change in total calories was 265.70 Kcal/day higher (42.94 to 488.46 Kcal/day higher) in the treatment group.	NA	58 (1 trial)	⊕⊕⊖⊖ **low[2,3]**	There was also a significant advantage to the treatment group over the control group at 6 months (MD 304.86 Kcal/day, 95% CI 5.62 kcal/day to 604.10 Kcal/day, 48 participants, 1 trial). There was no significant difference between treatment groups at 3 months (MD 115.09 Kcal/day, 95% CI -121.34 Kcal/day to 351.52 Kcal/day, 58 participants, 2 trials).
Change in total protein (g/day): at 12 months Follow-up: up to 12 months	The mean change in total protein was 5.75 g/day in the control group.	The mean change in total calories was 6.82 g/day higher (2.36 g/day lower to 16.00 g/day higher) in the treatment group.	NA	58 (1 trial)	⊕⊕⊖⊖ **low[2,3]**	There was also no significant difference between treatment groups at 3 months (MD 2.51 g/day, 95% CI -6.74 g/day to 11.77 g/day, 58 participants, 2 trials) or at 6 months (MD 8.77 g/day, 95% CI -1.24 g/day to 18.78 g/day, 48 participants, 1 trial).
Change in total fat (g/day): at 12 months Follow up: up to 12 months	The mean change in total fat was 12.23 g/day in the control group.	The mean change in total calories was 8.85 g/day higher (4.64 g/day lower to 22.34 g/day higher) in the treatment group.	NA	58 (1 trial)	⊕⊕⊖⊖ **low[2,3]**	There was also no significant difference between treatment groups at 3 months (MD -1.10 g/day, 95% CI -15.05 g/day to 12.85 g/day, 58 participants, 2 trials) or at 6 months (MD 11.74 g/day, 95% CI -2.96 g/day to 26.44 g/day, 48 participants, 1 trial).
Adverse events: Follow up: up to 12 months	See comment	See comment	NA	Not stated (1 trial)	⊕⊖⊖⊖ **very low[4]**	One trial investigated gastro-intestinal symptoms with a questionnaire and reported no significant difference between the groups.
Change in lung function - FEV_1 (% predicted): at 12 months Follow-up: up to 12 months	The mean change in FEV_1 (% predicted) was -1.5 in the control group.	The mean change in FEV_1 (% predicted) 1.91 lower (8.57 lower to 4.75 higher) in the treatment group.	NA	70 (1 trial)	⊕⊕⊖⊖ **low[2,5]**	There was a significant decline in FEV_1 (% predicted) in the treatment group compared to the control group at 3 months (MD -7.96, 95% CI -13.52 to -2.40). There was no significant difference between treatment groups at 6 months (MD -3.39, 95% CI -9.97 to 3.19). There was also no significant difference in change in FVC between treatment groups at 3, 6 and 12 months.

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (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).

BMI: body mass index; **CI**: confidence interval; **FEV_1**: forced expiratory volume at 1 second; **FVC**: forced vital capacity; **MD**: mean difference; **NA**: not applicable

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

1. There was also no significant difference in terms of other indices of nutrition or growth; weight for height (percentage) at 3 months, change in BMI (kg/m^2) at 3, 6 and 12 months and change in BMI centile at 3 and 12 months. There was a significant advantage for oral calorie supplements over control at 6 months (MD 5.75, 95% CI 0.22 to 11.28, 101 participants, 1 trial).
2. Downgraded once due to applicability; results apply only to children between the ages of 2 and 15 years, results not applicable to adults.
3. Downgraded once due to incomplete outcome data; 58 out of 102 children returned the 12 month dietary diary, 44 who did not return the diary are excluded from analysis.
4. Downgraded twice due to imprecision and once due to risk of selective outcome reporting bias; adverse events of treatment were reported in only a single trial and very limited information was provided about the rate of adverse events.
5. Downgraded once due to applicability; Spirometry data recorded only for children over the age of 5 years, lung function outcomes are not applicable to children between the ages of 2 to 5 years from this study.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is a multisystem disorder affecting many organs including the lungs, gastro-intestinal tract, pancreas and liver. Failure to thrive is a common means of presentation of undiagnosed children with CF; and poor nutrition may be a problem in the children and adults diagnosed with CF (Shepherd 1980). This may worsen as the disease progresses. In recent years guidelines have recommended that dietary intake should provide at least 120% of the recommended daily allowance for energy in people with cystic fibrosis (Sinaasappel 2002). This increased calorie requirement is contributed to by multiple factors. These include malabsorption and, in children or adults with more advanced chest disease, it may also be contributed to by increased work of breathing or chronic pulmonary sepsis. In addition, when unwell, people with CF may have reduced appetite. It was suggested by studies in the 1980s that there was an increased energy requirement associated with the basic defect of CF (Shepherd 1988), but this is now disputed and resting energy expenditure in clinical stable children with CF has been shown to be similar to control children without CF (Marin 2004). Poor nutrition has been associated with adverse outcomes in CF and therefore nutritional management is directed at maintaining normal weight and height for age in people with CF (MacDonald 1996). There is a further systematic review which assesses the effectiveness of this intervention for children with chronic disease (Francis 2015).

Description of the intervention

Oral calorie supplements (OCS) are usually in the form of either fortified milk or juice drinks or simple energy sources.

How the intervention might work

These supplements are used to try and increase the total daily calorie intake and thereby improve weight gain. Provided calorie supplements are taken in addition to normal dietary intake from food, then overall calorie intake should be improved.

Why it is important to do this review

However, it is possible that OCS may replace some of the calories taken as food and their potential effect on overall total calorie intake be either reduced or eliminated. A further potential adverse consequence of replacing calorie intake from normal food by calories from OCS may be to have a detrimental effect on normal eating behaviour, which is particularly critical in toddlers and young children who are learning to develop normal eating behaviour. In addition, OCS are expensive and therefore it is important to evaluate their effectiveness. The cost for a 10-year old child is about £1124 per annum in the UK (RLCH 2006).

This is an updated version of previously published reviews (Smyth 2000; Smyth 2007; Smyth 2012; Smyth 2014).

OBJECTIVES

To examine the evidence that in people with CF oral calorie supplements:

- improve measures of nutritional status, lung function and survival and quality of life;
- increase daily calorie intake, without reducing calorie intake from normal food;
- are associated with adverse effects in people with CF, which are either important to the individual or have long-term sequelae. These may include diarrhoea, reduced appetite, and bloating.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), published or unpublished. Trials, where quasi-randomisation methods such as alternation are used, would be included if there was sufficient evidence that the treatment and comparison groups were comparable in terms of clinical and nutritional status.

Types of participants

Children and adults with defined CF, diagnosed clinically and by sweat or genetic testing, including all ages and all degrees of severity, including severity of undernutrition.

Types of interventions

Oral calorie supplements, in the form of either fortified milk or juice drinks or as simple energy sources, given in any amount for a period of at least one month, where these have been compared to existing conventional therapies in people with CF. Existing conventional therapies may include nutritional advice on how to improve calorie input from food or no specific intervention. These two control groups will be analysed separately when there are sufficient studies available. Trials where OCS are used for reasons other than to increase calorie intake were excluded.

Types of outcome measures

Primary outcomes

1. Change in weight or height or body mass index (BMI) or z score or other indices of nutrition or growth

Secondary outcomes

1. Anthropometric measures of body composition
2. Total calorie intake measured daily or weekly or over some other time interval
3. Calorie intake from food measured daily, weekly or over some other time interval
4. Calorie intake from OCS measured daily, weekly or over some other time interval
5. Nutrient intake measured daily, weekly or at some other time interval
6. Measures of eating behaviour
7. Measures of quality of life
8. Adverse effects including diarrhoea, reduced appetite, abdominal bloating, episodes of distal intestinal obstruction syndrome and any other adverse effects reported
9. Measures of lung function
10. Number of deaths or age at death in each group
11. Activity levels (post hoc change)

Search methods for identification of studies

There will be no restrictions regarding language or publication status.

Electronic searches

Relevant trials were identified from the Group's Cystic Fibrosis Trials Register using the terms: calorie supplements AND oral.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTAL) (updated each new issue of the *Cochrane Library*), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Cystic Fibrosis and Genetic Disorders Group Module.

Date of the most recent search of the Group's CF Trials Register: 18 October 2016.

Searching other resources

In addition, full text searching of the *Journal of Pediatrics* from 1988 to 1996 was undertaken. Additional RCTs were found from the reference lists provided by the review group. Furthermore, the companies which manufacture OCS were contacted to ask whether they have data on RCTs of OCS in CF on file.

Data collection and analysis

Selection of studies

The two authors independently selected the trials to be included in the review. Any disagreements were resolved by discussion.

Data extraction and management

Each author independently extracted data and again any disagreements were resolved by discussion.

Outcome data were grouped into those measured at one, three, six, 12 months and annually thereafter. If outcome data were recorded at other time periods then consideration was given to examining these as well.

Assessment of risk of bias in included studies

In order to establish a risk of bias for each included trial, each author assessed the methodological quality of each trial. In particular, authors examined details of generation of the randomisation sequence and allocation concealment. If these were considered adequate the authors deemed the trial to be at low risk of bias. The authors also assessed whether the trial was blinded. The more people blinded to an intervention (participants, clinicians and outcome assessors), the lower the risk of bias would be for that trial. The authors also examined whether intention-to-treat analyses were possible from the available data and if the number of participants lost to follow up or subsequently excluded from the trial was recorded. Any trials which did not discuss or account for missing data or participants was thought to have a potential risk of bias. For quasi-randomised studies, each author examined the baseline characteristics of the intervention and comparison groups to assess whether the two groups were comparable. If groups were not comparable, there would be a risk of bias.

Measures of treatment effect

For binary outcome measures, we aimed to calculate a pooled estimate of the treatment effect for each outcome across trials (the odds of an outcome among treatment allocated participants to the corresponding odds among controls). For continuous outcomes, we recorded either mean change from baseline for each group or mean post-treatment/intervention values and standard deviation or standard error for each group. We aimed to calculate a pooled estimate of treatment effect by determining the mean difference (MD) and corresponding 95% confidence intervals (CIs).

Unit of analysis issues

We do not plan to include any cross-over trials as this design is not appropriate to assess the effect of the intervention or the above-mentioned outcomes.

Dealing with missing data

In order to allow an intention-to-treat analysis, we sought data on the number of participants with each outcome event, by allocated treated group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow up.

Where data were not available in the published trial reports, we contacted the lead investigator of the trial for further information.

Assessment of heterogeneity

We planned that heterogeneity between trial results would be tested for using a standard Chi^2 test.

Data synthesis

We analysed the data using a fixed-effect model. We had originally planned to analyse data using a random-effects model if we had identified significant heterogeneity between trials.

Subgroup analysis and investigation of heterogeneity

We originally planned to perform subgroup analyses stratified according to type of control group(s) used, age and severity of nutritional status.

Sensitivity analysis

We also planned to perform a sensitivity analysis based on the methodological quality of the trials, including and excluding quasi-randomised trials.

Summary of findings and assessment of the certainty of the evidence

In a post hoc change from protocol, we have presented a summary of findings tables for the comparison of oral calorie supplements compared to control (no intervention, dietary advice or nutritional counselling) for adults and children with CF (Summary of findings 1).

The following outcomes were reported in the tables (chosen based on relevance to clinicians and consumers): change in weight (kg), change in height (cm), change in total calories (kcal/day), change

in total protein (g/day), change in total fat (g/day), adverse events, lung function (change in per cent (%) predicted FEV_1). All outcomes are reported at 12 months.

We determined the quality of the evidence using the GRADE approach; and downgraded evidence in the presence of a high risk of bias in at least one study, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias. We downgraded evidence by one level if they considered the limitation to be serious and by two levels if very serious.

RESULTS

Description of studies

Results of the search

The searches for this review identified a total of 22 potentially eligible trials. Three trials were included in the review; 18 trials were excluded from the review; and one trial is awaiting classification.

Included studies

All three included trials (n = 131) have been published as abstracts and full papers (Hanning 1993; Kalnins 2005; Poustie 2006).

Trial design

Two trials were RCTs (Hanning 1993; Poustie 2006) and one was a quasi-RCT (Kalnins 2005). All three were of parallel design (Hanning 1993; Kalnins 2005; Poustie 2006). Two trials were single centre (Hanning 1993; Kalnins 2005) and one was multicentre with included participants recruited from 17 hospitals (Poustie 2006). All three trials had differing durations: in one the intervention was given for three months with a total of six months follow-up (Kalnins 2005); in the second trial the intervention was given for six months (Hanning 1993); and in the third trial, the intervention was given for 12 months (Poustie 2006).

One trial was an explanatory trial (Hanning 1993) (an explanatory trial is one which looks at biological mechanisms, rather than one which aims to provide sound treatment recommendations (Murray 1991)). The main aim of this trial was to investigate the relationship between nutritional status and skeletal muscle strength. Since they are investigating the biological effects of treatment, explanatory trials usually only analyse the information on individuals who completed treatment, which was the case in this trial. Two trials presented data using an ITT analysis (Kalnins 2005; Poustie 2006).

Participants

Numbers of participants ranged from 15 (Kalnins 2005) to 102 (Poustie 2006). Two trials enrolled children up to 15 years of age (Hanning 1993; Poustie 2006) and one trial included both children and adults (Kalnins 2005). In two studies there were almost equal numbers of males and females (Hanning 1993; Poustie 2006), but in one trial there were more females (n = 10) than males (n = 3) (Kalnins 2005).

All trials supplied details of participant characteristics at baseline (Hanning 1993; Kalnins 2005; Poustie 2006). In the Hanning trial, although the participants were described as having mild to moderate lung disease and were randomised with adequate allocation concealment, the treatment and control groups were not similar at baseline; the treatment group appearing to be in better clinical condition (Hanning 1993).

Two trials stated inclusion criteria: for the Kalnins trial these were below 90% ideal weight for height or a 5% reduction in ideal weight for height over three months (Kalnins 2005); and in the CALICO trial at least one of the following - a BMI below the 25th centile but over 0.4th centile, or no increase in weight over the previous three months, or a 5% decrease in weight from baseline over a period shorter than six months (Poustie 2006).

Interventions

The interventions in the included trials were targeted to achieve an increase in energy intake of 20% (Kalnins 2005; Poustie 2006) or 25% (Hanning 1993). Two trials compared dietary advice in addition to supplements in the form of drinks to dietary advice alone (Kalnins 2005; Poustie 2006). One trial compared the use of dietary supplements (drink powders, milk shakes or tinned puddings) to a control group receiving no additional supplements (Hanning 1993).

Outcomes

All three trials reported on dietary energy and nutrient intake, height, weight, anthropometric measurements and pulmonary function (Hanning 1993; Kalnins 2005; Poustie 2006). Two trials reported on activity levels (Hanning 1993; Poustie 2006). Hanning additionally reported on skeletal muscle strength and power, respiratory muscle strength and laboratory measures of nutritional status (e.g. albumin, amino acids) (Hanning 1993). Kalnins additionally reported weight for height scores and faecal balance studies (Kalnins 2005). Poustie reported BMI scores and gastro-intestinal symptoms (Poustie 2006).

Excluded studies

A total of 18 trials were excluded for a variety of reasons. Details can be found in the section Characteristics of excluded studies.

Seven trials did not use an oral calorie supplement in the intervention (Abdulhamid 2008; Bruzzese 2007; Ellis 1998; Haworth 2004; Lloyd-Still 2001; Oudshoorn 2007; Papas 2007). Four trials did not give an oral calorie supplement with the objective of increasing calorie intake (Best 2004; Caramia 2003; Grey 2003; Milla 1996). Three trials were of insufficient duration (less than one month) (Adde 1997; Kane 1991; Sondel 1987). One trial was not randomised (Patchell 2001) and a further trial was a quasi-RCT, but the groups were not comparable at baseline (Steinkamp 2000). One trial did not have a comparator group without an oral supplement (Lepage 2002) and in one trial the calorie supplement was not given orally (McKenna 1985).

Risk of bias in included studies

Allocation

In the trial by Hanning and the CALICO trial, generation of the randomisation sequence was based on a table of random numbers and so we judged these trials to have a low risk of bias (Hanning 1993; Poustie 2006). In the trial by Kalnins, participants were segregated by age and sex and the initial participants from each group were randomly allocated to intervention or control (Kalnins 2005). The paper does not give any details of how this randomisation was undertaken, so we deemed this trial to have an unclear risk of bias (Kalnins 2005).

Allocation in the Hanning trial and the CALICO trial was concealed using sealed envelopes and we judged these trials to have a low risk of bias (Hanning 1993; Poustie 2006). The trial by Kalnins was quasi-randomised, initial participants from each group were randomly allocated to intervention or control, then each subsequent participant was allocated a different group from the previous one (Kalnins 2005). We therefore judged this trial to have a potential risk of bias.

Blinding

Due to the interventions, blinding of clinicians and participants was not possible in any of the three included trials, but all three trials blinded the outcome assessors for some or all outcomes. In the Hanning trial, investigators performing skeletal and lung muscle-function tests and anthropometry were unaware of the participant's study group (Hanning 1993). In the CALICO trial, the researcher undertaking the analysis of outcomes was masked as to the allocation groups (Poustie 2006). These two trials were deemed to have some risk of bias. In the Kalnins trial apart from the 'study monitors' (nurse and dietitian), all other investigators were blinded (but it was not clear whether all investigators who assessed the outcome measures were blinded) (Kalnins 2005). Due to this fact the risk of bias for this trial is unclear.

Incomplete outcome data

In the Hanning trial, an intention-to-treat analysis was not performed (Hanning 1993); 20 participants were randomised but data from only 16 participants were presented. The paper does give reasons for the four participants withdrawing (they found the time demands for testing or the travelling distance to be excessive) (Hanning 1993). We therefore judged this trial to have a low risk of bias from incomplete outcome data.

In the Kalnins trial, two participants (one in each group) dropped out after completing baseline (reasons were feeling unwell and change of mind) and were not followed up (Kalnins 2005). Two out of seven participants allocated to the supplement group were not taking supplements at three months, but were included in the analysis, which was judged to be intention to treat (Kalnins 2005). We judged there to be some risk of bias in this trial since although the withdrawals were described and the analysis was by intention to treat, the drop outs were not equal across groups.

In the CALICO trial, analysis was by intention to treat (Poustie 2006). It was stated that all 102 children randomised completed the trial; however there were some data not available for some of the outcomes. Interim data on two children from the supplement group (due to parental choice or illness) and on one child from the standard care group (due to illness) were not collected. We judged there to be little risk of bias here as the drop outs were equal across groups and for similar reasons. Furthermore, nine children failed to return the baseline diet diary and 39 failed to return the 12-month diet diary (no details given for which group these children were allocated to), so dietary intake data are based on the 58 children who completed both diaries. Spirometry data are available for 70 of the 72 children who were aged over five years, again no details are given as to which group the two missing sets of data were from.

Selective reporting

Two trials had an unclear risk of bias as they did not report adverse events; however it was unclear if this was due to a lack of adverse events or a failure to report them (Hanning 1993; Kalnins 2005). Kalnins did not report the change from baseline values for outcome measures in the original publication, but has since provided summary statistics for the change from baseline to the authors of this review (Kalnins 2005). One trial was judged to have a low risk of bias for selective reporting as all outcomes described in the 'Methods' section of the full paper are reported in the 'Results' section (Poustie 2006).

Other potential sources of bias

In the Hanning trial, it was noted that the participants in the treated group appeared to be in better clinical condition at baseline than in the control group (Hanning 1993). This could potentially be a source of bias.

Effects of interventions

See: **Summary of findings 1** Summary of findings

It should be noted that the total number of participants included in this review was 131; 16 from one trial (Hanning 1993), 13 from the second trial (Kalnins 2005) and 102 from the third trial (Poustie 2006). In the Hanning trial, the groups were not similar at baseline, therefore we have not included these results. We have attempted, as yet unsuccessfully, to obtain further information from the authors, in particular the mean change from baseline for all outcomes relevant to the review and data on the four participants who dropped out, to enable an intention-to-treat analysis.

The majority of the participants in this review were from the CALICO trial. Where possible, the outcomes measured at three and six months from the Kalnins and Hanning trials are combined with the CALICO trial. All the outcomes reported at 12 months are from the CALICO trial (Poustie 2006).

Primary outcome

1. Change in weight or height or BMI or z score or other indices of nutrition or growth

a. Change in weight

There was no significant difference between the groups at any time point (Analysis 1.1); although data from two trials showed a trend for the supplement group to have greater improvement at three months, MD 0.32 kg (95% CI -0.09 to 0.72) (Kalnins 2005; Poustie 2006), and from two trials at six months MD 0.47 kg (95% CI -0.07 to 1.02) (Hanning 1993; Poustie 2006). However, this was not apparent from a single trial at 12 months, MD 0.16 kg (95% CI -0.68 to 1.00) (Poustie 2006).

b. Change in weight centile

Data were only available from one trial (Poustie 2006). There was no significant difference between the groups at three months, MD 1.72 percentile points (95% CI -0.59 to 4.03), at six months, MD 2.12 percentile points (95% CI -0.94 to 5.18) or 12 months, MD 1.83 percentile points (95% CI -1.77 to 5.43) (Analysis 1.2).

c. Change in height

There was no significant difference between the groups at three months (two trials (Kalnins 2005; Poustie 2006)), MD -0.04 cm (95% CI -0.36 to 0.29), at six months (one trial (Poustie 2006)), MD -0.47

cm (95% CI -1.32 to 0.38) or at 12 months (one trial (Poustie 2006)), MD 0.06 cm (95% CI -0.50 to 0.62) (Analysis 1.3).

d. Change in height centile

Data were only available from one trial (Poustie 2006). Analysis showed no significant difference between the groups at three months, MD -0.56 percentile points (95% CI -2.04 to 0.92), at six months, MD -1.74 percentile points (95% CI -4.40 to 0.92) or at 12 months, MD -0.65 percentile points (95% CI -3.11 to 1.81) (Analysis 1.4).

e. Weight for height

Data were only available from one trial (Kalnins 2005); at three months there was no significant difference between the groups, MD -0.96% (95% CI -5.23 to 3.31) (Analysis 1.5).

f. Change in BMI

Data were only available from one trial (Poustie 2006). There was no significant difference between the groups at three months, MD 0.14 kg/m^2 (95% CI -0.08 to 0.36), at six months, MD 0.24 kg/m^2 (95% CI -0.06 to 0.54) or at 12 months, MD 0.08 kg/m^2 (95% CI -0.28 to 0.44) (Analysis 1.6).

g. Change in BMI centile

Data were only available from one trial (Poustie 2006). There was no significant difference between the groups at three months, MD 3.28 percentile points (95% CI -0.70 to 7.26), at six months, MD 5.75 percentile points (95% CI 0.22 to 11.28) or at 12 months, MD 2.99 percentile points (95% CI -2.69 to 8.67) (Analysis 1.7).

Secondary outcomes

1. Anthropometric measures of body composition

a. Change in mid-upper arm circumference

Data were only available from one trial (Poustie 2006). There was no significant difference between the groups at three months, MD 0.19 cm (95% CI -0.25 to 0.63), at six months, MD 0.22 cm (95% CI -0.17 to 0.61) or at 12 months, MD 0.21 cm (95% CI -0.27 to 0.69) (Analysis 1.8).

2.Total calorie intake measured daily or weekly or over some other time interval

a. Change in total calorie intake

There was no significant difference between the groups at three months (two trials (Kalnins 2005; Poustie 2006)), MD 115.09 Kcal (95% CI -121.34 to 351.52) (Analysis 1.9). Data at six months and 12 months were only reported in one trial (Poustie 2006); these data showed that the total calorie intake recorded in the supplement group was greater; at six months, MD 304.86 Kcal (95% CI 5.62 to 604.10), and at 12 months, MD 265.70 Kcal (95% CI 42.94 to 488.46) (Analysis 1.9).

b. Change in total protein intake

There was no significant difference between the groups at three months (two trials (Kalnins 2005; Poustie 2006)), MD 2.51 g/day (95% CI -6.74 to 11.77), at six months (one trial (Poustie 2006)), MD 8.77 g/day (95% CI -1.24 to 18.78) or at 12 months (one trial (Poustie 2006)), MD 6.82 g/day (95% CI -2.36 to 16.00) (Analysis 1.10).

c. Change in total fat intake

There was no significant difference between the groups at three months (two trials (Kalnins 2005; Poustie 2006)), MD -1.10 g/day (95% CI 15.05 to 12.85), at six months (one trial (Poustie 2006)), MD 11.74 g/day (95% CI -2.96 to 6.44) or at 12 months (one trial (Poustie 2006)), MD 8.85 g/day (95% CI -4.64 to 22.34) (Analysis 1.11).

3. Calorie intake from food measured daily, weekly or over some other time interval

No study reported this outcome measure.

4. Calorie intake from OCS measured daily, weekly or over some other time interval

This outcome was only reported in one trial; at the three-month time point, mean (SD) calorie intake per day from supplements was 126.8 (387.7) Kcal in the supplement group (Kalnins 2005).

5. Nutrient intake measured daily, weekly or at some other time interval

No trial reported this outcome measure.

6. Measures of eating behaviour

No trial reported this outcome.

7. Measures of quality of life

No trial reported this outcome.

8. Adverse effects including diarrhoea, reduced appetite, abdominal bloating, episodes of distal intestinal obstruction syndrome and any other adverse effects reported

The CALICO trial investigated gastro-intestinal symptoms with a questionnaire and reported no significant difference between the groups (Poustie 2006).

9. Measures of lung function

a. Change in FEV_1 (% predicted)

At three months, the change in FEV_1 (% predicted) was greater in the control group (two trials (Kalnins 2005; Poustie 2006)), MD -7.96% (95% CI -13.52 to -2.40), but there was no significant difference between groups at six months (one trial (Poustie 2006)), MD -3.39% (95% CI -9.97 to 3.19) (Poustie 2006), or at 12 months (one trial (Poustie 2006)), MD -1.91% (95% CI -8.57 to 4.75) (Analysis 1.12).

b. Change in FVC (% predicted)

Data were only available from one trial (Poustie 2006). There was no significant difference between the groups at three months, MD 0.12% (95% CI -9.17 to 9.41), at six months, MD -0.13% (95% CI -9.07 to 8.81) or at 12 months, MD 5.27% (95% CI -3.67 to 14.21) (Analysis 1.13).

10. Number of deaths or age at death in each group

None of the trials reported any deaths.

11. Activity levels (post-hoc change)

Data were only available from one trial (Poustie 2006). There was no significant difference between the groups at three months, MD 0.52% in 24 hours (95% CI -3.89 to 4.93), at six months, MD -1.84%

in 24 hours (95% CI -6.38 to 2.70) or at 12 months, MD -0.08% in 24 hours (95% CI -4.05 to 3.89) (Analysis 1.14).

DISCUSSION

Summary of main results

This Cochrane Review has shown that use of oral protein energy supplements does not improve nutritional status in people with cystic fibrosis (CF). It suggests that dietary advice alone is a satisfactory approach to the management of people with CF and moderate malnutrition. This has implications for the nutritional management of CF as these products are widely prescribed and are expensive. We feel that oral protein calorie supplements should not be regarded as an essential part of the long-term clinical care of children with CF who are moderately malnourished.

Overall completeness and applicability of evidence

There are some issues which should be considered when assessing the implications of the review for clinical practice. Firstly, the result of this review was largely contributed to by the CALICO study (Poustie 2006). This study was conducted in children, not adults, who were moderately malnourished and the intervention given was in the form of oral protein energy supplements, taken as drinks, over the long term. The children generally had good lung function (mean forced expiratory volume in one second (FEV_1) % predicted was greater than 70%) and did not have severe complications of CF. Therefore one must be cautious in considering whether the results of this review can be applied to adults with more severe lung disease or worse nutritional status or both. Additionally, the short-term use of nutritional supplements as a strategy to treat acute weight loss was not assessed in any other trial included in this review.

Total energy and macronutrient intake in the included trials were assessed by information from diaries. The investigators in the CALICO trial reviewed this carefully and felt that the diary information was likely to be an overestimate of the participants' intake from supplements, as supplement groups seemed to be consuming about 18% more than the standard care group relative to their estimated average requirement for energy intake, but showed no change in nutritional status. Hence reported intake of food and other nutrients by participants should be interpreted with caution in clinical studies.

Quality of the evidence

The quality of the evidence was judged to be moderate for the change in weight and height and low for the change in total calories, total fat and total protein intake (this is because results are applicable only to children between the ages of two and 15 years and many post-treatment diet diaries were not returned). Evidence for the rate of adverse events in the treatment groups was extremely limited and judged to be of very low quality.

Potential biases in the review process

The authors undertook comprehensive searching for this review so there is unlikely to be any bias due to the non-identification of relevant trials. However, the lead author of the review was also an investigator on the largest included study in the review. To avoid any potential bias from this fact data from that study were extracted and checked by an independent person at the editorial base.

Agreements and disagreements with other studies or reviews

Despite the findings of this review, guidelines from the USA (CFF 2016) and the UK (UK CF Trust 2010; UK CF Trust 2013) continue to provide recommendations for their use, although the statements made are not specific about the clinical situation in which they should be used. A non-Cochrane systematic review states, "For children with growth deficits and adults with weight deficits, the CF Foundation recommends the use of nutritional supplements (oral and enteral) in addition to usual dietary intake to improve the rate of weight gain" (Stallings 2008), but does not reference this Cochrane Review or the CALICO trial (Poustie 2006).

AUTHORS' CONCLUSIONS

Implications for practice

In children with CF who are moderately malnourished the use of dietary advice and monitoring alone is an appropriate approach to management. Nutritional supplements may be used but should not be regarded as an essential part of care.

Implications for research

The place of oral protein energy supplements in the short-term management of people with CF and acute weight loss should be assessed in randomised controlled trials. The place of this intervention in the long-term management of adults with CF or people with advanced lung disease, or both, should also be assessed in randomised controlled trials.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Hanning 1993

Study characteristics	
Methods	Random allocation using sealed envelopes. Parallel design, no intention-to-treat analysis. Duration: 6 months. Location: single centre in Canada.
Participants	20 children with CF and mild to moderate lung disease, aged 7 - 15 years. Lung function (FEV_1 % predicted) (mean (SD)): control group 84.2% (26.3); supplemented group 101.4% (19.4). % WFH (mean (SD)); control group 95.6% (12.1); supplement group 92.8% (11.3). 20 randomised (12 males), 16 (10 males) studied.

Hanning 1993 *(Continued)*

Interventions	Dietary supplements, drink powders, milk shakes, tinned puddings to achieve 25% of normal energy recommendations in addition to normal diet. No intervention in control groups.
Outcomes	Skeletal muscle strength and power Pulmonary function* and respiratory muscle strength Height*, weight* and anthropometric measurements* Habitual physical activity Body composition Dietary energy* and nutrient intake* Energy* and nutrient* intake from supplements Laboratory measures of nutritional status (e.g. albumin, amino acids)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation using based on a table of random numbers.
Allocation concealment (selection bias)	Low risk	Used sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Investigators performing skeletal and lung muscle-function tests and anthropometry were unaware of the participant's study group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No ITT analysis. 20 randomised, 16 studied. Four participants did not complete the trial because they found the time demands for testing or the travelling distance to be excessive.
Selective reporting (reporting bias)	Unclear risk	No adverse events reported; not clear if no events occurred or if not reported.
Other bias	High risk	The treated group appeared to be in better clinical condition at baseline.

Kalnins 2005

Study characteristics

Methods	Quasi-randomised controlled trial. Parallel design. Duration: 3 months. Location: single centre in Canada.
Participants	CF participants aged > 10 years. Age on entry to trial: advice group mean (SD) 16.4 years (6.7); supplement group mean (SD) 19.5 years (11.3). < 90% ideal WFH or 5% reduction in ideal WFH over 3 months. Most recent published report states 15 were enrolled but 2 dropped out. Gender split: 3/13 were males.

Kalnins 2005 *(Continued)*

	Although 2 out of 7 in the supplement group did not continue taking supplements, they were analysed as ITT.
Interventions	High calorie drink to increase energy intake by 20% of predicted energy needs. Control group received nutritional counselling to increase energy intake by 20% of predicted energy needs by eating high calorie foods.
Outcomes	Z scores for weight* and height*, WFH* Anthropometric measures* Pulmonary function* Energy* and nutrient* intake Faecal balance studies
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quasi-randomised controlled trial: participants were segregated by age and sex, initial participants from each group randomly allocated to intervention or control (paper does not state how initial randomisation occurred), then each subsequent participant was allocated a different group from the previous one.
Allocation concealment (selection bias)	High risk	Inadequate, used alternate allocation.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not possible to blind dietitian or participant - it was stated that apart from the 'study monitors' (nurse and dietitian), all other investigators were blinded, but it was not clear whether all investigators who assessed the outcome measures were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants dropped out, one in each group after completing baseline (reasons included feeling unwell and change of mind) and were not followed up; 2 out of 7 participants allocated to the supplement group were not taking supplements at 3 months, but were included in the analysis, which was judged to be ITT.
Selective reporting (reporting bias)	Unclear risk	No adverse events reported; not clear if no events occurred or if not reported. Did not report the change from baseline values for outcome measures in the original publication, but has since provided summary statistics for the change from baseline to the authors of this review.
Other bias	Unclear risk	Unable to make clear judgement.

Poustie 2006

Study characteristics

Methods	Randomised controlled trial. Parallel design. Duration: 12 months. Location: multicentre in UK.

Poustie 2006 *(Continued)*

Participants	102 children (54 males) aged 2 - 15 years with CF and at least one of following criteria: BMI < 25th centile but > 0.4th centile; or no increase in weight over the previous 3 months; or 5% decrease in weight from baseline over a period of < 6 months.
Interventions	Oral calorie supplements (range of different brands used, but daily amount to increase usual energy intake by 20%) plus routine dietetic advice compared with dietary advice alone.
Outcomes	Change in BMI* Change in BMI percentile* Change in weight* Change in height* Change in weight percentile* Change in height percentile* Mid-upper arm circumference* Energy* and macro-nutrient* intake FEV_1 and FVC expressed as % predicted for age, sex and height* Gastro-intestinal symptoms* Outcomes measured at 3, 6 and 12 months. All participants were followed up to 12 months.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Generation of the randomisation sequence used random number tables.
Allocation concealment (selection bias)	Low risk	Used sealed opaque envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Not possible to blind clinicians and participants, but the researcher undertaking the analysis of outcomes was masked as to the allocation groups.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis was by ITT. All 102 randomised children completed the trial. However, unable to collect interim data on 2 children from the supplement group (owing to parental choice or illness) and 1 child from the standard care group (illness). Nine children failed to return the baseline diet diary, and 39 failed to return the 12-month diet diary, so dietary intake data are based on the 58 children who completed both baseline and 12 month diaries. Spirometry data available for 70 of the 72 participants aged 5 and above.
Selective reporting (reporting bias)	Low risk	All outcomes described in the Methods section of the published paper (including adverse events) reported on.
Other bias	Low risk	No other potential source of bias identified.

*Outcomes to be included in review
BMI: body mass index
CF: cystic fibrosis
FEV_1: forced expiratory volume in 1 second
ITT: intention-to-treat
SD: standard deviation
WFH: weight for height

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

Study	Reason for exclusion
Abdulhamid 2008	Intervention is zinc supplementation, not an OCS.
Adde 1997	Intervention was only given in hospital and while it does not explicitly state the duration of the intervention it is highly unlikely to meet our inclusion criteria of at least one month. Furthermore, there is no evidence of randomisation.
Best 2004	OCS not given to increase calorie intake.
Bruzzese 2007	Intervention is a pro-biotic, not an OCS.
Caramia 2003	OCS not given to increase calorie intake.
Ellis 1998	The products used were formula-based infant milks and not OCS.
Grey 2003	Supplements used for reasons other than to increase calorie input.
Haworth 2004	Intervention is calcium and vitamin D supplements, not an OCS.
Kane 1991	OCS taken for less than one month. Both groups received OCS.
Lepage 2002	No comparison with a group not receiving OCS.
Lloyd-Still 2001	Intervention not an OCS.
McKenna 1985	Supplements not given orally.
Milla 1996	OCS not given to increase calorie intake. OCS given for period less than one month.
Oudshoorn 2007	Intervention uses micronutrient supplements not OCS.
Papas 2007	Pharmacokinetic trial of different formulations of vitamin E supplementation, not OCS.
Patchell 2001	Not a randomised controlled trial.
Sondel 1987	OCS taken for less than one month. Both intervention groups received supplements.
Steinkamp 2000	Groups not comparable at the start of the study and quasi-randomised design.

OCS: oral calorie supplements

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

MacDonald 2001

Methods	Randomised parallel study comparing supplementation with control in CF.
Participants	People with CF.
Interventions	Supplementary feed 'Healthshake'.
Outcomes	Growth and biochemistry.

MacDonald 2001 *(Continued)*

Notes	Publication ID: N0045006074. Title: Evaluation of supplementary feed (Healthshake) in the nutritional management of children with cystic fibrosis. NRR data provider: Birmingham Children's Hospital NHS Foundation Trust.

CF: cystic fibrosis

DATA AND ANALYSES

Comparison 1. Oral calorie supplements versus no intervention or additional nutritional advice

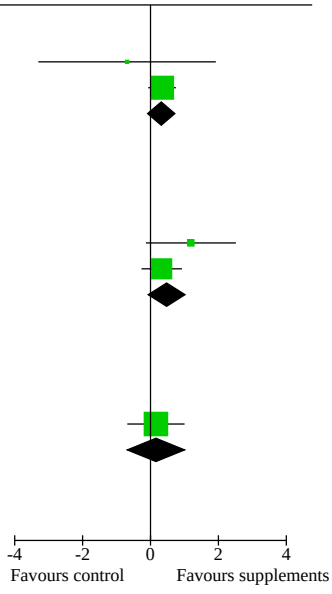
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Change in weight (kg)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1.1 3 months	2	112	Mean Difference (IV, Fixed, 95% CI)	0.32 [-0.09, 0.72]
1.1.2 6 months	2	117	Mean Difference (IV, Fixed, 95% CI)	0.47 [-0.07, 1.02]
1.1.3 12 months	1	102	Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.68, 1.00]
1.2 Change in weight centile (percentile points)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2.1 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2.2 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2.3 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3 Change in height (cm)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.3.1 3 months	2	112	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.36, 0.29]
1.3.2 6 months	1	101	Mean Difference (IV, Fixed, 95% CI)	-0.47 [-1.32, 0.38]
1.3.3 12 months	1	102	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.50, 0.62]
1.4 Change in height centile (percentile points)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4.1 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4.2 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4.3 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.5 Change in weight for height (percentage)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.5.1 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 Change in BMI (kg/m2)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6.1 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6.2 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6.3 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7 Change in BMI centile (percentile points)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7.1 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7.2 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7.3 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8 Change in mid-upper arm circumference (cm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8.1 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8.2 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8.3 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9 Change in total Kcal/day	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.9.1 3 months	2	58	Mean Difference (IV, Fixed, 95% CI)	115.09 [-121.34, 351.52]
1.9.2 6 months	1	48	Mean Difference (IV, Fixed, 95% CI)	304.86 [5.62, 604.10]
1.9.3 12 months	1	58	Mean Difference (IV, Fixed, 95% CI)	265.70 [42.94, 488.46]
1.10 Change in total protein (g)/day	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.10.1 3 months	2	58	Mean Difference (IV, Fixed, 95% CI)	2.51 [-6.74, 11.77]
1.10.2 6 months	1	48	Mean Difference (IV, Fixed, 95% CI)	8.77 [-1.24, 18.78]
1.10.3 12 months	1	58	Mean Difference (IV, Fixed, 95% CI)	6.82 [-2.36, 16.00]
1.11 Change in total fat (g)/day	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.11.1 3 months	2	58	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-15.05, 12.85]
1.11.2 6 months	1	48	Mean Difference (IV, Fixed, 95% CI)	11.74 [-2.96, 26.44]
1.11.3 12 months	1	58	Mean Difference (IV, Fixed, 95% CI)	8.85 [-4.64, 22.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.12 Change in FEV_1 (% predicted)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.12.1 3 months	2	82	Mean Difference (IV, Fixed, 95% CI)	-7.96 [-13.52, -2.40]
1.12.2 6 months	1	70	Mean Difference (IV, Fixed, 95% CI)	-3.39 [-9.97, 3.19]
1.12.3 12 months	1	70	Mean Difference (IV, Fixed, 95% CI)	-1.91 [-8.57, 4.75]
1.13 Change in FVC (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.13.1 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.13.2 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.13.3 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.14 Change in activity (% 24 hours)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.14.1 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.14.2 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.14.3 12 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

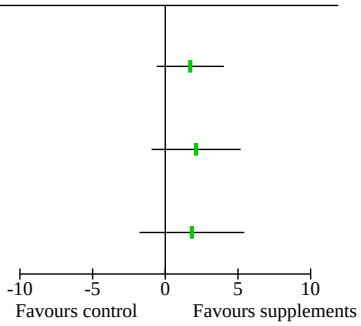
Analysis 1.1. Comparison 1: Oral calorie supplements versus no intervention or additional nutritional advice, Outcome 1: Change in weight (kg)

Study or Subgroup	Supplements Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 3 months								
Kalnins 2005	1.46	2.15	7	2.15	2.59	6	2.4%	-0.69 [-3.30 , 1.92]
Poustie 2006	1.11	1.25	48	0.77	0.73	51	97.6%	0.34 [-0.07 , 0.75]
Subtotal (95% CI)			**55**			**57**	**100.0%**	**0.32 [-0.09 , 0.72]**
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%								
Test for overall effect: Z = 1.54 (P = 0.12)								
1.1.2 6 months								
Hanning 1993	2.52	1.33	9	1.33	1.35	7	16.8%	1.19 [-0.13 , 2.51]
Poustie 2006	2.05	1.8	50	1.72	1.18	51	83.2%	0.33 [-0.26 , 0.92]
Subtotal (95% CI)			**59**			**58**	**100.0%**	**0.47 [-0.07 , 1.02]**
Heterogeneity: Chi² = 1.35, df = 1 (P = 0.25); I² = 26%								
Test for overall effect: Z = 1.71 (P = 0.09)								
1.1.3 12 months								
Poustie 2006	3.13	2.35	50	2.97	1.97	52	100.0%	0.16 [-0.68 , 1.00]
Subtotal (95% CI)			**50**			**52**	**100.0%**	**0.16 [-0.68 , 1.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.37 (P = 0.71)								



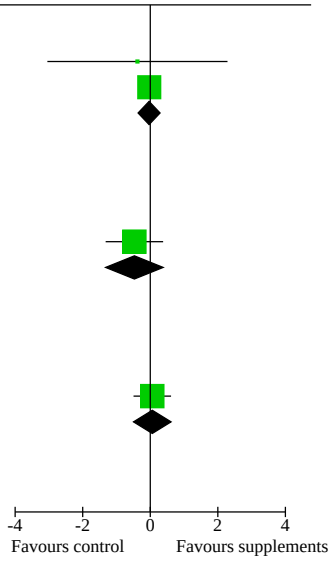
Analysis 1.2. Comparison 1: Oral calorie supplements versus no intervention or additional nutritional advice, Outcome 2: Change in weight centile (percentile points)

Study or Subgroup	Supplements Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.2.1 3 months							
Poustie 2006	2.12	6.58	48	0.4	4.98	51	1.72 [-0.59 , 4.03]
1.2.2 6 months							
Poustie 2006	2.75	9.56	50	0.63	5.6	51	2.12 [-0.94 , 5.18]
1.2.3 12 months							
Poustie 2006	0.83	10.96	50	-1	7.14	52	1.83 [-1.77 , 5.43]



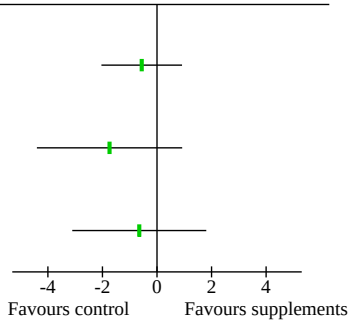
Analysis 1.3. Comparison 1: Oral calorie supplements versus no intervention or additional nutritional advice, Outcome 3: Change in height (cm)

Study or Subgroup	Supplements Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 3 months								
Kalnins 2005	2.17	2.54	7	2.55	2.36	6	1.5%	-0.38 [-3.05 , 2.29]
Poustie 2006	1.65	0.86	48	1.68	0.8	51	98.5%	-0.03 [-0.36 , 0.30]
Subtotal (95% CI)			**55**			**57**	**100.0%**	**-0.04 [-0.36 , 0.29]**
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.80); I² = 0%								
Test for overall effect: Z = 0.21 (P = 0.83)								
1.3.2 6 months								
Poustie 2006	3.09	1.03	50	3.56	2.92	51	100.0%	-0.47 [-1.32 , 0.38]
Subtotal (95% CI)			**50**			**51**	**100.0%**	**-0.47 [-1.32 , 0.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.08 (P = 0.28)								
1.3.3 12 months								
Poustie 2006	5.91	0.85	50	5.85	1.85	52	100.0%	0.06 [-0.50 , 0.62]
Subtotal (95% CI)			**50**			**52**	**100.0%**	**0.06 [-0.50 , 0.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.21 (P = 0.83)								



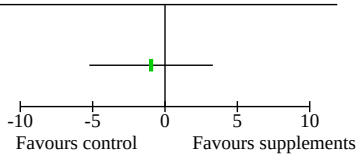
Analysis 1.4. Comparison 1: Oral calorie supplements versus no intervention or additional nutritional advice, Outcome 4: Change in height centile (percentile points)

Study or Subgroup	Supplements Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.4.1 3 months							
Poustie 2006	0.57	3.69	48	1.13	3.81	51	-0.56 [-2.04 , 0.92]
1.4.2 6 months							
Poustie 2006	0.24	0.27	50	1.98	9.7	51	-1.74 [-4.40 , 0.92]
1.4.3 12 months							
Poustie 2006	0.53	6.94	50	1.18	5.62	52	-0.65 [-3.11 , 1.81]



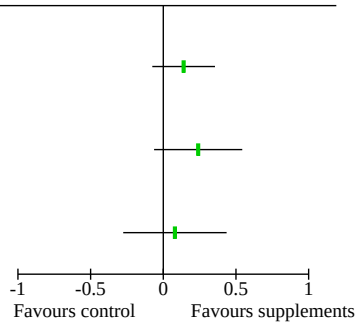
Analysis 1.5. Comparison 1: Oral calorie supplements versus no intervention or additional nutritional advice, Outcome 5: Change in weight for height (percentage)

Study or Subgroup	Supplements Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.5.1 3 months							
Kalnins 2005	0.71	4.5	7	1.67	3.33	6	-0.96 [-5.23 , 3.31]



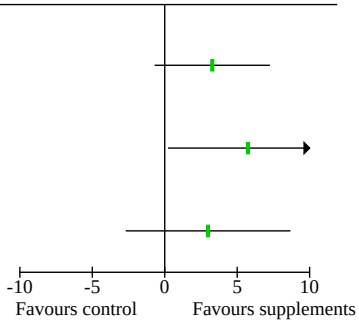
Analysis 1.6. Comparison 1: Oral calorie supplements versus no intervention or additional nutritional advice, Outcome 6: Change in BMI (kg/m2)

Study or Subgroup	Supplements Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.6.1 3 months							
Poustie 2006	0.19	0.65	48	0.05	0.41	51	0.14 [-0.08 , 0.36]
1.6.2 6 months							
Poustie 2006	0.39	0.87	50	0.15	0.67	51	0.24 [-0.06 , 0.54]
1.6.3 12 months							
Poustie 2006	0.32	1.03	50	0.24	0.78	52	0.08 [-0.28 , 0.44]



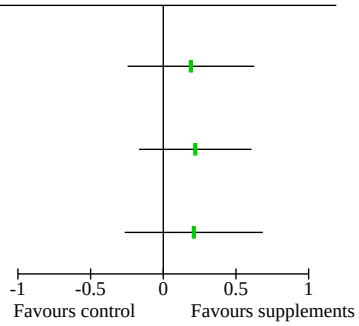
Analysis 1.7. Comparison 1: Oral calorie supplements versus no intervention or additional nutritional advice, Outcome 7: Change in BMI centile (percentile points)

Study or Subgroup	Supplements Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.7.1 3 months							
Poustie 2006	2.72	11.42	48	-0.56	8.47	51	3.28 [-0.70 , 7.26]
1.7.2 6 months							
Poustie 2006	4.46	15.5	50	-1.29	12.66	51	5.75 [0.22 , 11.28]
1.7.3 12 months							
Poustie 2006	0.67	18.2	50	-2.32	9.63	52	2.99 [-2.69 , 8.67]



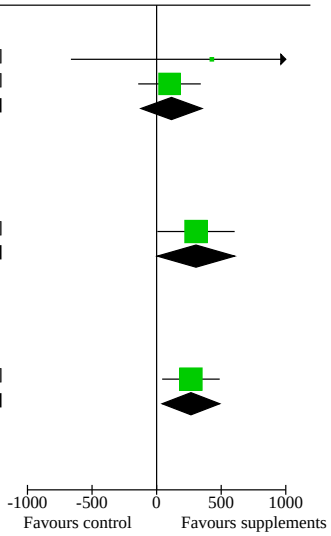
Analysis 1.8. Comparison 1: Oral calorie supplements versus no intervention or additional nutritional advice, Outcome 8: Change in mid-upper arm circumference (cm)

Study or Subgroup	Supplements Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.8.1 3 months							
Poustie 2006	0.44	1.41	48	0.25	0.64	51	0.19 [-0.25 , 0.63]
1.8.2 6 months							
Poustie 2006	0.57	1.24	50	0.35	0.65	51	0.22 [-0.17 , 0.61]
1.8.3 12 months							
Poustie 2006	0.68	1.44	50	0.47	0.95	52	0.21 [-0.27 , 0.69]



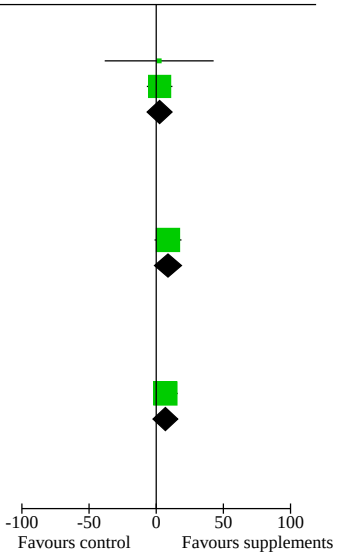
Analysis 1.9. Comparison 1: Oral calorie supplements versus no intervention or additional nutritional advice, Outcome 9: Change in total Kcal/day

Study or Subgroup	Supplements Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.9.1 3 months								
Kalnins 2005	384.6	1094.5	7	-43	912.7	6	4.7%	427.60 [-663.61 , 1518.81]
Poustie 2006	290.24	409.33	21	190.54	418.27	24	95.3%	99.70 [-142.48 , 341.88]
Subtotal (95% CI)			**28**			**30**	**100.0%**	**115.09 [-121.34 , 351.52]**
Heterogeneity: Chi² = 0.33, df = 1 (P = 0.57); I² = 0%								
Test for overall effect: Z = 0.95 (P = 0.34)								
1.9.2 6 months								
Poustie 2006	365.19	585.72	27	60.33	471.88	21	100.0%	304.86 [5.62 , 604.10]
Subtotal (95% CI)			**27**			**21**	**100.0%**	**304.86 [5.62 , 604.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.00 (P = 0.05)								
1.9.3 12 months								
Poustie 2006	405.22	371.2	27	139.52	492.18	31	100.0%	265.70 [42.94 , 488.46]
Subtotal (95% CI)			**27**			**31**	**100.0%**	**265.70 [42.94 , 488.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.34 (P = 0.02)								



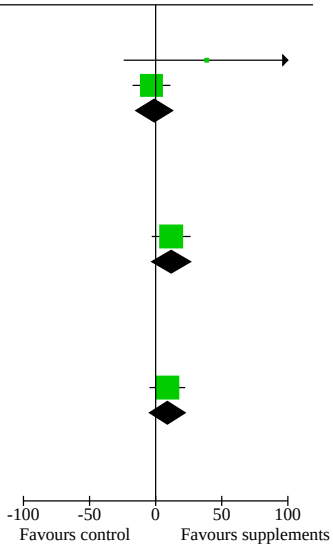
Analysis 1.10. Comparison 1: Oral calorie supplements versus no intervention or additional nutritional advice, Outcome 10: Change in total protein (g)/day

Study or Subgroup	Supplements Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.10.1 3 months								
Kalnins 2005	13	45.9	7	10.8	27.6	6	5.2%	2.20 [-38.34 , 42.74]
Poustie 2006	10.4	16.51	21	7.87	15.91	24	94.8%	2.53 [-6.98 , 12.04]
Subtotal (95% CI)			**28**			**30**	**100.0%**	**2.51 [-6.74 , 11.77]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%								
Test for overall effect: Z = 0.53 (P = 0.59)								
1.10.2 6 months								
Poustie 2006	13.98	20.32	27	5.21	15.07	21	100.0%	8.77 [-1.24 , 18.78]
Subtotal (95% CI)			**27**			**21**	**100.0%**	**8.77 [-1.24 , 18.78]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.72 (P = 0.09)								
1.10.3 12 months								
Poustie 2006	12.57	16.41	27	5.75	19.27	31	100.0%	6.82 [-2.36 , 16.00]
Subtotal (95% CI)			**27**			**31**	**100.0%**	**6.82 [-2.36 , 16.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.46 (P = 0.15)								



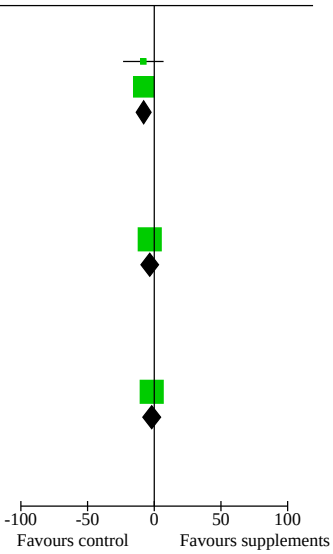
Analysis 1.11. Comparison 1: Oral calorie supplements versus no intervention or additional nutritional advice, Outcome 11: Change in total fat (g)/day

Study or Subgroup	Supplements Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.11.1 3 months								
Kalnins 2005	11.7	54.6	7	-26.9	60	6	4.9%	38.60 [-24.18 , 101.38]
Poustie 2006	11.93	23.9	21	15.09	25.03	24	95.1%	-3.16 [-17.47 , 11.15]
Subtotal (95% CI)			**28**			**30**	**100.0%**	**-1.10 [-15.05 , 12.85]**
Heterogeneity: Chi² = 1.62, df = 1 (P = 0.20); I² = 38%								
Test for overall effect: Z = 0.15 (P = 0.88)								
1.11.2 6 months								
Poustie 2006	14.06	28.27	27	2.32	23.66	21	100.0%	11.74 [-2.96 , 26.44]
Subtotal (95% CI)			**27**			**21**	**100.0%**	**11.74 [-2.96 , 26.44]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.57 (P = 0.12)								
1.11.3 12 months								
Poustie 2006	21.08	24.56	27	12.23	27.86	31	100.0%	8.85 [-4.64 , 22.34]
Subtotal (95% CI)			**27**			**31**	**100.0%**	**8.85 [-4.64 , 22.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.29 (P = 0.20)								



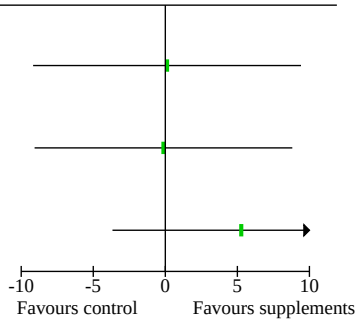
Analysis 1.12. Comparison 1: Oral calorie supplements versus no intervention or additional nutritional advice, Outcome 12: Change in FEV_1 (% predicted)

Study or Subgroup	Supplements Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.12.1 3 months								
Kalnins 2005	-6.6	14.6	7	1.6	13.3	6	13.4%	-8.20 [-23.37 , 6.97]
Poustie 2006	-2.55	12.28	31	5.37	12.97	38	86.6%	-7.92 [-13.89 , -1.95]
Subtotal (95% CI)			**38**			**44**	**100.0%**	**-7.96 [-13.52 , -2.40]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%								
Test for overall effect: Z = 2.81 (P = 0.005)								
1.12.2 6 months								
Poustie 2006	-1.78	11.51	32	1.61	16.45	38	100.0%	-3.39 [-9.97 , 3.19]
Subtotal (95% CI)			**32**			**38**	**100.0%**	**-3.39 [-9.97 , 3.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.01 (P = 0.31)								
1.12.3 12 months								
Poustie 2006	-3.41	13.5	32	-1.5	14.89	38	100.0%	-1.91 [-8.57 , 4.75]
Subtotal (95% CI)			**32**			**38**	**100.0%**	**-1.91 [-8.57 , 4.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.56 (P = 0.57)								



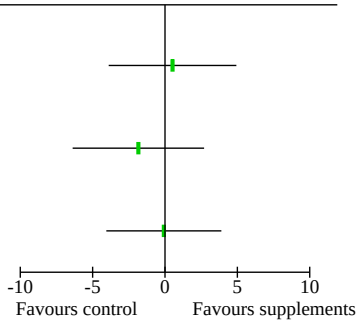
Analysis 1.13. Comparison 1: Oral calorie supplements versus no intervention or additional nutritional advice, Outcome 13: Change in FVC (% predicted)

Study or Subgroup	Supplements Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.13.1 3 months							
Poustie 2006	1.47	13.98	30	1.35	24.31	37	0.12 [-9.17 , 9.41]
1.13.2 6 months							
Poustie 2006	-3	17.71	31	-2.87	20.16	38	-0.13 [-9.07 , 8.81]
1.13.3 12 months							
Poustie 2006	0.06	17.82	31	-5.21	20.02	38	5.27 [-3.67 , 14.21]



Analysis 1.14. Comparison 1: Oral calorie supplements versus no intervention or additional nutritional advice, Outcome 14: Change in activity (% 24 hours)

Study or Subgroup	Supplements Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.14.1 3 months							
Poustie 2006	-0.34	9.86	47	-0.86	12.36	51	0.52 [-3.89 , 4.93]
1.14.2 6 months							
Poustie 2006	-3.43	10.62	50	-1.59	12.6	51	-1.84 [-6.38 , 2.70]
1.14.3 12 months							
Poustie 2006	-4.97	9.77	50	-4.89	10.7	52	-0.08 [-4.05 , 3.89]



WHAT'S NEW

Date	Event	Description
8 April 2021	Review declared as stable	Due to a lack of research in this area the Editorial Board of the Cystic Fibrosis and Genetic Disorders Review Group have decided to no longer update this review.

HISTORY

Protocol first published: Issue 1, 1997
Review first published: Issue 1, 1998

Date	Event	Description
26 April 2017	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register identified a single new reference which was potentially eligible for inclusion in this review and which has been excluded (Adde 1997).

Date	Event	Description
		A summary of findings table has been added to the review.
26 April 2017	New citation required but conclusions have not changed	As no new data have been added at this update, our conclusions remain the same.
27 October 2014	New search has been performed	A search of the Cystic Fibrosis & Genetic Disorders Review Group's Cystic Fibrosis Trials Register did not identify any new studies for possible inclusion in this review. The Plain Language Summary has been updated to reflect new guidance on style.
27 October 2014	New citation required but conclusions have not changed	A new author has joined the review team (Oli Rayner) after a previous author has stepped down from the review. As no new trials have been included in this updated review, our conclusions remain the same.
17 October 2012	Amended	Contact details updated.
4 September 2012	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register did not identify any new references eligible for inclusion in this review.
4 September 2012	New citation required but conclusions have not changed	No new references have been added to the review at this update, therefore the conclusions of this review remain the same.
15 September 2010	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register did not identify any new references which were potentially eligible for inclusion in this review.
12 August 2009	Amended	Contact details updated.
20 August 2008	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified two new references. One of these was an additional reference to an already excluded study (Abdulhamid 2008); the other reference was excluded as the intervention was not an oral calorie supplement (Bruzzese 2007).
19 August 2008	Amended	Converted to new review format.
13 November 2007	Amended	The Plain Language Summary has been re-drafted in light of the latest guidance from The Cochrane Collaboration.
13 November 2007	New search has been performed	The search identified two new references both of which have been added to the list of excluded studies (Oudshoorn 2007; Papas 2007).
15 November 2006	New search has been performed	The search identified ten new references to five trials. One reference was to an already included trial (Kalnins 2005). A further trial has now been included in the review (Poustie 2006). The other three trials have been added to 'Excluded studies' (Abdulhamid 2005; Haworth 2004; Lloyd-Still 2001).
15 November 2006	New citation required and conclusions have changed	Substantive amendment

Date	Event	Description
15 November 2006	Amended	A post hoc change has been made to the list of secondary outcomes and 'Activity levels' has now been added.
18 August 2004	New search has been performed	The search identified three new references. One of these was an additional reference to a study already excluded (Grey 2003). The other references were to two studies, both of which were excluded (Best 2004; Caramia 2003).
20 August 2003	New search has been performed	Three references have been added to the 'Excluded studies' section (McKenna 1985; Lands 2000; Lepage 2002). One reference has been added to the 'Ongoing studies' section (CALICO trial 2003).
11 July 2002	New search has been performed	A search of the Group's trials register found no new trials eligible for inclusion in this review.

CONTRIBUTIONS OF AUTHORS

Rosalind Smyth and Sarah Walters wrote the protocol and independently assessed studies for inclusion in this review. Rosalind Smyth extracted the data and wrote the remainder of the text. Rosalind Smyth wrote the updates of this review with comments from Sarah Walters (up to 2012) and from Oli Rayner (from 2014 onwards).

Rosalind Smyth acts as guarantor of this review.

DECLARATIONS OF INTEREST

Professor Rosalind Smyth was principle investigator in the CALICO trial which is included in this review.

Oli Rayner acts as a consultant to the UK Cystic Fibrosis Trust, a charitable organisation which supports basic and clinical research in cystic fibrosis. He has carried out work on this review on a *pro bono* basis and it is entirely unrelated to any work with the UK Cystic Fibrosis Trust. The UK Cystic Fibrosis Trust has no financial interest in the outcome of this review and nor does he.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In November 2006, a post hoc change was made to the list of secondary outcomes and 'Activity levels' was added.

NOTES

Please refer to the following Cochrane Review, which assesses the effectiveness of this intervention for children with chronic disease:

Francis DK, Smith J, Saljuqi T, Watling RM. Oral protein calorie supplementation for children with chronic disease. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD001914. DOI: 10.1002/14651858.CD001914.pub2.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Child Nutrition Disorders [*diet therapy] [etiology]; Cystic Fibrosis [*complications]; *Dietary Supplements [adverse effects]; *Energy Intake; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans