

personnel, and significant sponsors. The survey data book originates with WHO MONICA Project investigators and thousands of participants.

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## Oral protein energy supplements for children with cystic fibrosis: CALICO multicentre randomised controlled trial

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### Abstract

**Objective** To determine whether oral protein energy supplements, used long term in children with cystic fibrosis who are moderately malnourished, improve nutritional and other outcomes.

**Design** Multicentre randomised controlled trial.

**Setting** Seven specialist paediatric cystic fibrosis centres and their associated shared care clinics and seven smaller paediatric cystic fibrosis clinics.

**Participants** 102 children with cystic fibrosis, aged between 2 and 15 years, who were moderately malnourished.

**Interventions** Oral protein energy supplements in addition to usual dietary advice compared with dietary advice alone, for 12 months.

**Main outcome measure** Change in body mass index centile over one year.

**Results** Use of supplements was not associated with a change in body mass index centile (mean difference 2.99 centile points, 95% confidence interval -2.70 to 8.68) or other nutritional and spirometric outcomes in this group of children.

**Conclusions** Long term use of oral protein energy supplements did not result in an improvement in nutritional status or other clinical outcomes in children with cystic fibrosis who were moderately malnourished. Oral protein energy supplements should not be regarded as an essential part of the management of this group of children.

**Trial registration** ISRCTN: 95744468.

### Introduction

Poor nutrition is common in people with cystic fibrosis and is an important predictor of decline in lung function.<sup>1-5</sup> Oral protein energy supplements are

widely prescribed to improve energy intake and nutritional status.<sup>6</sup> However, many people find them unpalatable, particularly when prescribed for long term use. A systematic review of oral protein energy supplements for people with cystic fibrosis identified two eligible trials involving 29 participants.<sup>7</sup> Because of a lack of evidence, the review was unable to reach a conclusion on the efficacy of these supplements.


The aim of the CALICO (calories in cystic fibrosis—oral) trial was to investigate whether oral protein energy supplements improve or prevent deterioration in the body mass index centile of children with cystic fibrosis. The trial also evaluated the effect of supplements on other measures of nutritional status, macronutrient intake, spirometric lung function, activity levels, and gastrointestinal symptoms.

### Methods

#### Study design and participants

The trial was a multicentre randomised controlled trial of oral protein energy supplements for children with cystic fibrosis. We recruited children with cystic fibrosis aged between 2 and 15 years if they met one of the following criteria: body mass index of less than the 25th centile and more than the 0.4th centile, no increase in weight over the previous three months, a 5% decrease in weight from baseline over a period of less than six months. Children were recruited by dietitians at seven specialist cystic fibrosis centres in the United Kingdom, associated shared care clinics, and seven smaller clinics.

 Members of Trial Steering Committee and Collaborative Group are on [bmj.com](http://bmj.com)

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## Interventions

We provided the children with a selection of supplements to try before randomisation. We randomised those who found the supplements palatable to receive either oral protein energy supplements plus routine dietetic advice (supplement group) or routine dietetic advice alone (standard care group) for one year. We did not randomise children who did not find the supplements palatable. The children selected the supplements that they liked, and we recommended a daily amount sufficient to increase usual energy intake by 20%. We assessed all outcomes at baseline and at three, six, and 12 months.

## Outcomes

The primary outcome was change in body mass index centile over 12 months. We measured weight and height, and we calculated energy and macronutrient intake from four day, unweighed diet diaries.<sup>8</sup> We measured spirometric lung function, and we used the habitual activity estimation scale to assess activity levels.<sup>9</sup> We monitored self reported gastrointestinal symptoms.<sup>10</sup>

## Randomisation and statistical analysis

Randomisation was stratified within each centre. The research assistant was not blinded to allocation group, but a blinded investigator converted weight and height to body mass index centile.<sup>11</sup> The children in the trial were not blinded, because we had no satisfactory placebo.

A blinded analyst did the analysis by intention to treat. We calculated differences in mean change in body mass index centile and all other outcomes over 12 months between the supplement and standard care groups.

## Results

Twenty seven dietitians from 21 hospitals recruited 132 of 160 eligible children to the trial. We randomised 102 children recruited from 17 hospitals, 50 to the supplement group and 52 to the standard care group. Baseline characteristics of the two groups of children were balanced (see [bmj.com](http://bmj.com)).

All children were followed up to 12 months. We found no difference in mean change in body mass index centile from baseline to 12 months between the supplement group and the standard care group (mean difference 2.99 (95% confidence interval -2.70 to 8.68) centile points) (table, fig 1). No significant differences at these time points existed between the groups for weight and height centiles or for any other anthropometric outcomes.

We based dietary intake data on 58 children who completed both baseline and 12 month diaries. We found no differences between mean change from baseline to 12 months for dietary intake outcomes, apart from energy intake expressed as a percentage of that recommended for age and sex (mean difference 17.85 (5.11 to 30.58) percentage points), as shown in the table. We found no significant differences between the groups for any lung function outcomes and no differences between the groups in the activity diaries and gastrointestinal symptoms questionnaires (table).

Change in outcomes over 12 months. Values are means (SDs) unless stated otherwise

Outcome measure	Supplement group	Standard care group	Mean difference (95% CI)	P value
BMI centile	0.67 (18.20)	-2.32 (9.63)	2.99 (-2.70 to 8.68)	0.30
Weight centile	0.83 (10.96)	-1.00 (7.14)	1.83 (-1.79 to 5.45)	0.32
Height centile	-0.53 (6.94)	1.18 (5.62)	-0.65 (-3.12 to 1.83)	0.61
Mid-arm muscle circumference	0.76 (1.37)	0.62 (1.00)	0.14 (-0.34 to 0.61)	0.08
FEV <sub>1</sub> (% predicted)	-3.41 (13.50)	-1.50 (14.89)	-1.91 (-8.73 to 4.93)	0.58
FVC (% predicted)	0.06 (17.82)	-5.21 (20.02)	5.28 (-3.93 to 14.48)	0.26
Activity (% of day active)	-4.97 (9.77)	-4.89 (10.70)	-0.07 (-4.1 to 3.96)	0.97
Energy intake (% EAR)	24.48 (22.87)	6.63 (25.21)	17.85 (5.11 to 30.58)	0.01
Gastrointestinal symptom score	-0.42 (2.05)	-0.62 (2.03)	0.20 (-0.61 to 1.00)	0.63

BMI=body mass index; EAR=estimated average requirement for age and sex; FEV<sub>1</sub>=forced expiratory volume in 1 second; FVC=forced vital capacity.

## Discussion

These data suggest that oral protein energy supplements prescribed over one year, compared with dietary advice alone, did not result in a clinically important change in body mass index centile or other nutritional outcomes in children with cystic fibrosis. Addition of our trial data to the systematic review of oral protein energy supplements for people with cystic fibrosis clearly shows the limited efficacy of these products (fig 2).

One of our outcomes related to whether the prescription of oral protein energy supplements improved energy intake, as we were concerned that drinking these products would reduce energy intake from food. A marked improvement in energy intake seemed to occur in the supplement group, who consumed about 18% more than the standard care group, relative to their estimated average requirement for energy intake. We made conservative assumptions that, in this group, efficiency of energy storage is 50% and energy content of new tissue is 6000 kcal/kg and calculated that, if this difference in energy intake was maintained over one year, the average weight would be 10 kg greater in the supplement group. The actual mean difference in weight between the groups was

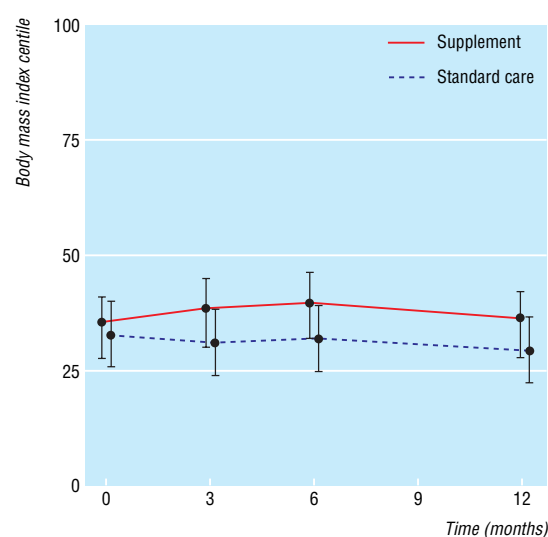
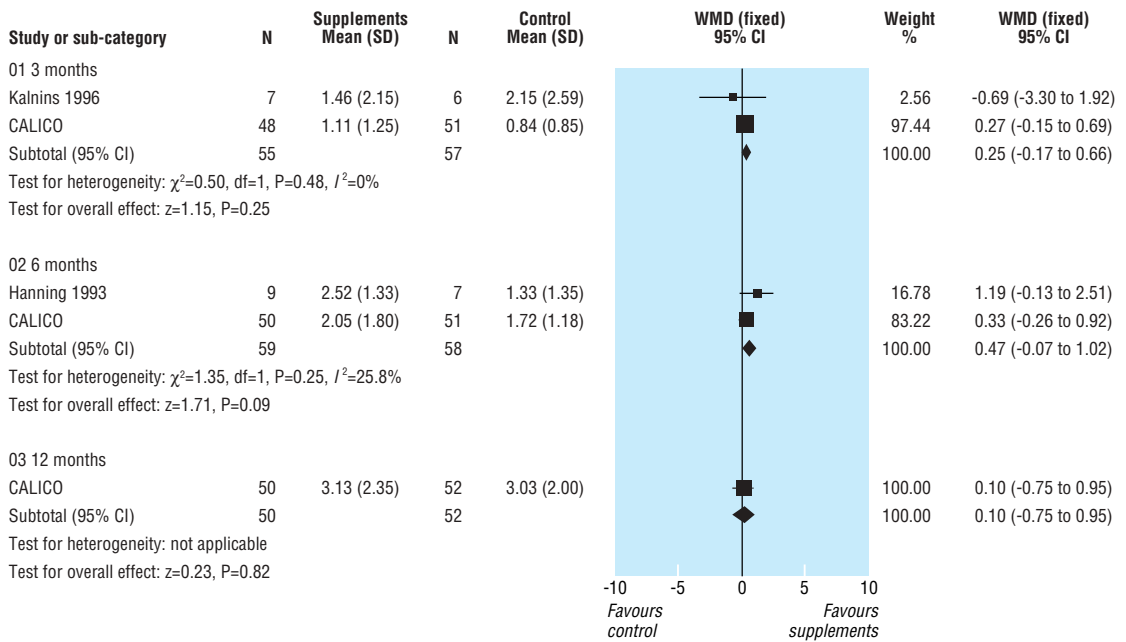


Fig 1 Body mass index centile over one year, by treatment group (lines show means; error bars show 95% confidence intervals)

Review: Oral calorie supplements for cystic fibrosis  
 Comparison: 01 Oral supplements versus no intervention or additional nutritional advice  
 Outcome: 01 Change in weight in kg



**Fig 2** Forrest plot showing effect of oral protein energy supplements, compared with no intervention or additional nutritional advice, on change in weight—adjusted to include evidence from CALICO trial (adapted from Cochrane systematic review of oral calorie supplements for cystic fibrosis<sup>7</sup>). WMD=weighted mean difference

0.17 kg (95% confidence interval -0.68 to 1.02 kg), which led us to conclude that the diet diary data are inaccurate. Energy intake data derived from diet diaries are acknowledged to show considerable inaccuracies compared with an objective measure.<sup>12</sup> It seems likely that children prescribed supplements overestimated their intake of supplements, food, or both in the diet diaries.

Longitudinal studies in children with cystic fibrosis have shown that weight, adjusted for age, is an independent predictor of percentage forced expiratory volume in one second some years later.<sup>4-5</sup> This study provides important reassurance that children who do not receive supplements, because they either are not prescribed them or do not like them, will not have a consequent decline in nutritional status, with potentially serious long term consequences.

The lack of effectiveness of supplements may be because children do not take them or because they reduce their food intake as a result of taking them. Because of concerns about the inaccuracies in the diet diaries, we have not attempted to assess this further. However, these influences are likely to be similar across different disease groups, and we suggest that trials to assess the effectiveness of nutritional supplements should be done in children with any chronic disease associated with poor nutritional status and growth failure.

**Conclusion**

When children with suboptimal nutrition receive regular dietary advice, their nutritional status is similar whether or not they have supplements. Although oral protein energy supplements may have a place in the treatment of malnourished children, possibly during

episodes of acute weight loss, they should not be regarded as an essential part of clinical care.

We thank the children with cystic fibrosis who participated in this trial and their families; Tim Cole, Jim Littlewood, John Reilly, and members of UK CF Dietitians Interest Group for advice on this study; and Larry Lands for allowing us to use the habitual activity estimation scale.

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**What is already known on this topic**

Oral protein energy supplements are often prescribed to improve growth and nutritional status in children with cystic fibrosis and other chronic conditions

These supplements are expensive, and many children do not like taking them regularly

Evidence from randomised controlled trials for the effectiveness of supplements is lacking

**What this study adds**

Long term use of oral protein energy supplements does not improve nutritional status in children with cystic fibrosis

Dietary advice alone is a satisfactory approach to the management of children with cystic fibrosis and moderate malnutrition

design of the trial, analysis of the results, or reporting of the findings.

Competing interests: VJP, RMW, JER, and several of the dietitians involved in this study have previously received travel expenses to attend conferences from the following manufacturers of oral protein energy supplements: SHS International, Liverpool, UK; Ross Laboratories, IL, USA; Nutricia, Trowbridge, UK; Nestle UK, Croydon.

Ethical approval: Ethical approval was granted by the North West Multi-centre Research Ethics Committee and by the local research ethics committees of all the collaborating centres.

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## Applicability to primary care of national clinical guidelines on blood pressure lowering for people with stroke: cross sectional study

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### Abstract

**Objective** To compare the characteristics of patients with cerebrovascular disease in primary care with those of the participants in the PROGRESS trial, on which national guidelines for blood pressure lowering are based.

**Design** Population based cross sectional survey of patients with confirmed stroke or transient ischaemic attack.

**Setting** Seven general practices in south Birmingham, England.

**Participants** All patients with a validated history of stroke (n = 413) or transient ischaemic attack (n = 107).

**Main outcome measures** Patient characteristics: age, sex, time since last cerebrovascular event, blood pressure, and whether receiving antihypertensive treatment.

**Results** Patients were 12 years older than the participants in PROGRESS and twice as likely to be women. The median time that had elapsed since their cerebrovascular event was two and a half years, compared with eight months in PROGRESS. The systolic blood pressure of 315 (61%) patients was over 140 mm Hg, and for 399 (77%) it was over 130 mm Hg. One hundred and forty seven (28%) patients were receiving a thiazide diuretic, and 136 (26%) were receiving an angiotensin converting enzyme inhibitor.

**Conclusions** Important differences exist between the PROGRESS trial participants and a typical primary care stroke population, which undermine the applicability of the trial's findings. Research in appropriate populations is urgently needed before

the international guidelines are implemented in primary care.

### Introduction

International guidelines stress the importance of lowering blood pressure in people who have had a stroke.<sup>1-4</sup> In the United Kingdom, for example, the national clinical guidelines for stroke recommend a target blood pressure of 140/85 mm Hg and that further lowering of blood pressure beyond this target should be aimed for by using a thiazide diuretic and an angiotensin converting enzyme inhibitor.<sup>1</sup> The British Hypertension Society guidelines are more aggressive, recommending a target blood pressure of 130/80 mm Hg.<sup>2</sup> The guidelines are heavily influenced by the PROGRESS trial, which recruited people with stroke from hospital settings.<sup>5</sup> Despite some debate about the implementation of these research findings regarding which drugs should be used,<sup>6</sup> a question that has been neglected is whether these guidelines are relevant to primary care, which is where most treatment of blood pressure occurs. We aimed to compare the characteristics of people who have had a stroke in primary care with those of the PROGRESS trial participants.

### Methods

We recruited seven practices active in research from the South Birmingham Primary Care Trust. The practices had a population of 37 000 and were selected to

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