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Review

Nutritional intervention in patients with Cystic Fibrosis: A systematic review

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Abstract

Background: To systematically assess the literature published after 1997 describing the effectiveness of nutritional interventions in Cystic Fibrosis patients.
Methods: An online search in PUBMED, EMBASE and COCHRANE databases was conducted. Original studies with 4 patients or more, describing a nutritional intervention and giving at least weight as an outcome parameter were included.
Results: The inclusion criteria were met by 17 articles, focusing on respectively behavioural interventions (n=6), oral supplementation (n=4) or enteral tube feeding (n=7). This latter intervention was universally successful to induce weight gain. One behavioural study and 2 oral supplementation studies also reported significant weight gain.
Conclusion: Enteral tube feeding is effective to improve nutritional status, while the described effects of behavioural intervention and oral supplementation are not consistent at present.

Keywords: Diet; Body size; Gastrostomy; Cystic Fibrosis; Nutrition assessment

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Abbreviations: CF, Cystic Fibrosis; FEV_1% pred., Forced expiratory volume in 1 s expressed as % of predicted; RDA, Recommended daily allowances; BMI, Body-mass-index.

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1. Introduction

Cystic Fibrosis (CF) is the most common lethal genetic disorder in Caucasians, affecting 1 in 4750 live births [1]. It is characterized by a gradual decline in pulmonary function, intestinal malabsorption and often an impaired nutritional status. Lung disease and nutritional status are tightly intertwined [2] and both are strong predictors of morbidity and mortality in patients with CF [1,3,4]. Malnutrition, due to a negative energy balance, is a common problem caused by a combination of faecal fat losses and increased energy requirements due to chronic infections [5]. Therefore, dietary guidelines prescribe that patients with CF should attain up to 200% of the recommended daily caloric intake [6,7]. However, this can be difficult to achieve because patients may have reduced appetite, infection-related anorexia, gastro-oesophageal reflux or abdominal pain. In this respect nutritional interventions can be helpful to increase caloric intake. In 1997, Jelalian et al. described in a meta-analysis that all nutritional interventions aimed at gaining weight were successful, including behavioural modifications, oral supplementation, enteral tube feeding as well as parenteral nutrition [8]. As CF treatment, and thus the nutritional status of patients has changed during the last 15 years [9,10], effectiveness of nutritional interventions might have changed too. Therefore, we have conducted a systematic review of the literature published after 1997, describing the current effectiveness of interventions aimed at enhancing nutritional status in patients with CF.

2. Methods

An online search in PUBMED, EMBASE and COCHRANE Central Register of Controlled Trials was carried out for all available articles published from the 1st of January 1997 up to April 30th, 2012. The search query was: 'Cystic Fibrosis' [MESH] AND 'Nutritional Status' [MESH], 'Cystic Fibrosis' [MESH] AND 'Diet' [MESH], 'Cystic Fibrosis' [MESH] AND ('Body Size' [MESH] OR 'Body Weight' [MESH]), 'Cystic Fibrosis' [MESH] AND 'Gastrostomy' [MESH] OR 'Enteral Nutrition' [MESH]. With this latter search term also studies using (nasogastric) tube feeding were identified. The reference lists of eligible articles and review articles were examined for additional studies. Excluded were articles concerning animals, non-English or non-Dutch articles, editorials, reviews, meta-analyses, articles with no abstract available and articles with a minimal sample size of three subjects or less. The search yielded 361 articles which were screened on title and abstract, and considered suitable if a nutritional intervention, with the aim to improve weight in CF patients, was described. Studies conducted in subgroups only, such as patients with CF related diabetes, were excluded. This resulted in 119 publications that were potentially eligible, which were subsequently screened on full text. To pass this final screening it was necessary that the clinical outcome included a weight variable, either absolute weight, z-score weight, weight-percentile, weight percentage, weight-for-height or body-mass-index (BMI), as a result of the treatment applied. Finally 17 articles were appropriate and included in this review. These studies described interventions involving behavioural modification aimed at increasing caloric intake, prescription of oral supplements or enteral tube feeding through a gastrostomy.

The following data were extracted: the name of the first author, country and year of publication, study design, the intervention offered for nutritional rehabilitation, duration of the intervention, size and, if available, gender and age distribution of the study population, initial weight, caloric intake, the duration of follow-up and, if described, pulmonary function assessed as forced expiratory volume in 1 s, expressed as percentage of predicted (FEV_1% pred.). The primary outcome measurement was the change in weight, either expressed as absolute weight in kilogramme, weight-for-age z-score, weight percentile, percentage weight-for-age, percentage of ideal-body-weight, percentage of weight-for-height, absolute body-mass-index (BMI) in kg/m^2, percentage BMI or BMI z-score. The secondary outcome measurement was the change in caloric intake per day and/or forced expiratory volume in 1 s expressed as % of predicted (FEV_1% pred.), if described.

3. Results

Nutritional interventions were subdivided into behavioural intervention (n=6) [11–16], oral supplementation (n=4) [17–20] and enteral tube feeding (n=7) [21–27]. The treatment length of the behavioural interventions ranged from 7 weeks [13–15] to one year [11] and the follow-up period from 1 year [11,12,16] to 2 years [13–15]. In two oral supplementation

Table 1
Characteristics of behavioural studies.

First author, country, year of study, study design	Type of intervention	Context of intervention	Sample characteristics	Results growth parameters	Caloric intake	FEV_1% predicted
Watson, UK, 2008 [16] Randomised controlled trial (34 (I) vs. 34 (C) patients)	Behavioural home-based nutritional education programme vs. standard care Patients were treated	Treatment length: 10 weeks Follow-up: 1 y outpatient	N=68 Male=40 Mean age (y): I: 25.2/C: 23.8 Nutritional status: BMI: I: 21.0/C: 21.6 During follow-up 4 patients died, 12 defaulted from follow-up, 3 withdrawn from study and 1 moved.	Baseline: weight (kg): I: 59.1±9.7/C: 59.4±10.0// BMI: I: 21.0/C: 21.6 After 6 mo: weight (kg): I (N=28): 59.5±10.0/ C (N=32): 60.2±10.8 (p=0.13) After 12 mo: weight (kg): I (N=23): 59.9±9.7/ C (N=25): 60.6±11.2 (p=0.18)// BMI: I: 21.3/C: 21.1 NS	ND	Baseline: I: 52.6±25.3/ C: 59.09±22.3 After 6 mo: I: 54.9±25.1/ C: 59.9±20.8 (p=0.576) After 12 mo: I: 52.8±24.1/ C: 58.3±21.5 (p=0.621)
Powers, US, 2003 [11] Randomised controlled trial (4 (I) vs. 4 (C) patients) *Pilot study*	Behavioural+nutritional counselling vs. nutritional counselling only Only parents treated	Treatment length: 1 y outpatient	N=8 Male=ND Age: <3 y Nutritional status: % weight-for-age: 42	Baseline: % weight-for-age: I: 42.0±13.9/C: 16.7±18.4//weight (kg): I: 11.6±1.3/C: 10.1±2.1 Post-treatment: % weight-for-age: I: 46.2±8.2/C: 21.5±9.0//weight (kg): I: 14.1±1.9/C: 12.8±2.0 NS	Kcal/day//% RDA Baseline: I: 1020.6±182.3// % RDA: 78.5±14.0/ C: 1030.8±146.2//% RDA: C: 79.0±11.2 Post-treatment: I: 1426.6±284.2//% RDA: 109.7±21.9 (p=0.07)/ C: 1316.2±227.3//% RDA: 101.2±17.5 NS	ND
Powers, US 2005 [12] Randomised controlled trial (4 (I) vs. 6 (C) patients) Afterwards 5 patients from control group underwent behavioural+nutritional intervention to replicate the effects	Behavioural intervention combined with nutritional counselling vs. standard care Parents were treated	Treatment length: 8 weeks Follow-up: 1 y outpatient	N=10 Male=6 Age (mo): 22–43 Mean age (mo): 31.5±6.2 Nutritional status: z-score weight-for-age −0.19±0.85	Baseline: weight z-score: I: −0.30±0.7/C: 0.08±1.0 After 12 mo (N=9): weight gain velocity: I: 2.5±0.96 kg/C: ND (for child of same age at 50th percentile for weight normal is 2 kg/12 mo)	Kcal/day Baseline: I: 1393.1±118/ C: 1387.3±105 Post-treatment: I: 2235.1±706/ C: 1256.0±215 (p=0.011)/caloric intake increase: I: 842/C: −131 After 3 mo (N=7): 1990.3±337 (p<0.001)/caloric intake increase: 672 After 12 mo (N=8): 2068.5±484 (p<0.001)/caloric intake increase: 750 Second sample control group: 5 patients from control group crossed over to behavioural nutritional intervention: Baseline: 1258.7±240 Post-treatment: 2151.5±301 (p=0.03)	ND

Stark, US, 2003 [13] Randomised controlled trial (3 (I) vs. 4 (C) patients)	Behavioural intervention combined with nutritional education vs. nutritional education only Both parents+patients were treated	Pre-treatment length: 1 week Treatment length: 7 weeks Follow-up: 2 y outpatient	N=7 Male=ND Age (y): 6–12 Mean age (y): 10 Nutritional status: weight-for-age below 40th percentile	Baseline weigh-for-age: 12th percentile, range 3rd–27th percentile Post-treatment: weight gain (kg): I: 1.48/C: 0.78 After 6 mo: I: 3.45/C: 1.45 After 12 mo: I: 5.23/C: 2.97 After 24 mo: I: 7.57/C: 7.32 Weight percentile: I: 2 of 3 increased, 1 stayed on 4th percentile/C: 2 of 4 declined, 1 stable, 1 increased.	Kcal/day Baseline increase: I: 1829/C: 1806 Post-treatment increase: I: 1036 (±401)/C: 408 (±410) After 24 mo: I: mean 946 kcal above baseline C: mean 313 kcal above baseline	Baseline: mean 95% (range 75% to 145%)
Stark, US, 2009 [14] Randomised controlled trial (33 (I) vs. 34 (C) patients)	Behavioural intervention combined with nutritional education vs. nutritional education only Both parents+patients were treated	Pre-treatment length: 2 weeks Treatment length: 7 weeks Follow-up: 2 y outpatient	N=67 Male=35 Age (y): 4–12 Mean age (y): 7.64 Nutritional status: weight for age below 40th percentile During follow-up 12 measurements were missed, 7 patients were dropped	Baseline weight (kg): I: 21.79±6.44/C: 22.62±7.45 BMI z-score: I: −0.77±1.12/C: −0.49±0.71 Post-treatment: weight (kg): I: 23.26±7.1/C: 23.54±7.78// Weight changes (kg) I: 1.47±1.27/C: 0.55±1.16 (p=0.01) BMI z-score: I: −0.39±1.08/C: −0.31±0.81//BMI changes: I: 0.38±0.46/C: 0.20±0.47 (p=0.03) After 24 mo (compared to pre-treatment): Weight (kg): I (N=28): 28.51±9.77/C (N=31): 29.51±10.84 Weight changes (kg): I: 6.97±3.6/C: 6.45±3.67 NS BMI z-score: I: −0.56±0.9/C: −0.71±0.66 BMI changes: I: 0.13±0.81/C: −0.22±0.5 NS	Kcal/day Baseline: I: 1793±350/C: 1826±476 Post-treatment: I: 2655±553/C: 2315±549 Caloric intake increase: I: 872±478/C: 489±314 (p<0.001) After 24 mo (compared to pre-treatment): I (N=26): 2523±620/C (N=25): 2411±577 Caloric intake increase: I: 721±522/C: 533±436 NS	Baseline: I (N=17): 88±18/C (N=13): 92±18 After 24 mo: I (N=18): 87±18/C (N=15): 87±17 NS
Stark, US, 2011 [15] Retrospective controlled cohort study (67 (I) vs. 346 (C) patients) I is intervention and control group from Stark et al. 2009	Behavioural intervention and/or nutritional education vs. standard care Both parents+patients were treated	Pre-treatment length: 2 weeks Treatment length: 7 week Follow-up: 2 y outpatient	N=67 (control group N=346) Male=35 (186) Age (y): 4–12 Mean age (y): 7.64 Nutritional status: weight for age below 40th percentile	Baseline BMI z-score: I: −0.63±0.94/C: −0.47±0.85 After 24 mo post-treatment: BMI z-score: I: −0.05±0.68/C: −0.21±0.67 Decline in BMI z-score significantly less in I group (p<0.0001)	ND	Baseline: I (N=36): 89.95±17.79/C (N=173): 87.71±20.16 After 24 mo post-treatment: I: 88.74/C: 84.45 I: decrease 1.21/C: decrease 3.25 NS

I=intervention group C=control group RDA=recommended daily allowances P-values from original studies added when available ND=not described NS=not significant

Table 2
Characteristics of oral supplementation studies.

First author, country, year of study, study design	Type of intervention	Context of intervention	Sample characteristics	Results Growth parameters	Caloric intake	FEV_1% predicted
Skypala, UK, 1998 [19] Single group Controlled trial (26 patients)	Oral supplement: flavoured powder which has to be constructed with full-fatty milk (2 kcal/ml) Aim of increasing energy intake by 20% of the patients' pre-trail energy intake	Treatment length: pre-treatment: 4 weeks Treatment: 8 weeks outpatient	N=26 Male=16 Mean age (y): 18.5 (9–34) Age ≤ 18 y (N=15) Inclusion criteria: Age<16 y: ideal weight-for-height below 95% or recently a weight loss of 5% of their usual weight Age>16 y: BMI less than 19	Pre-treatment: weight (kg): 43.8 (24.6–59.9)/ weight-for-height (% of predicted): 90.6 Baseline, after 4 weeks pre-treatment weight (kg): 43.7 (26–59.6)/ weight-for-height (% of predicted): 90.7 Week 12 (end of the intervention) weight (kg): 45.6 (27.7–59.3) (p<0.01)/ weight-for-height (% of predicted): 94.8	Pre-treatment: 120% RDA After 12 weeks: 143% RDA (p<0.01)	ND
Steinkamp, Germany, 2000 [20] Prospective randomised controlled trial (16 patients oral energy supplement+dietary counselling (I) vs. 20 patients dietary counselling (C))	Oral supplement: Energy supplement (1.0 kcal/ml, 31 En% fat, 16 En% protein) Aim: optimize energy intake by closing gap between calculated ideal and actual energy intake with supplement.	Treatment length: 3 mo Follow-up: 3 mo outpatient	N=36 Male=20 Mean age (y): I: 10.4±4.3 C: 13.3±3.8 Inclusion criteria: Weight-for-height below 95% of reference value	Baseline: weight (kg): I: 32.2±8.9/C: 27.3±7.6 Weight-for-height (% of predicted): I: 82.8±8.6/C: 87.8±8.7 After 3 mo: weight (kg) I: 33.4±9.6 (p<0.05)/C: 27.5±7.5 Weight-for-height (% of predicted) I: 84.8±9.6 (p<0.01)/	Baseline (kcal/day): I: 2189±731 C: 1881±507 After 3 mo: I: 2733±762 (p<0.01)/C: 1928±468	Baseline: I: 52±22/ C: 54±25 After 3 mo: I: 51±26/ C: 53±20 NS

Kalnins, Canada, 2005 [17] Randomised controlled trial (7 patients oral dietary supplementation (I) vs. 6 patients dietary counselling (C))	Oral supplement: Energy supplement (1.5 kcal/ml) Aim of increasing energy intake by 20% of predicted energy needs over a 3 mo period	Treatment length: 3 mo Follow-up: 3 mo outpatient	N=13 Male=3 Mean age (y) I: 19.5±11.3 C: 16.4±6.7 Inclusion criteria Below 90% of ideal-body-weight or 5% reduction in % ideal-body-weight in 3 mo	Baseline: z-score weight-for-age: I: −1.2±0.5/C: −0.8±0.8 % ideal-body-weight: I: 86±8/C: 83±10 After 3 mo: z-score weight-for-age: I: −1.1±0.7/C: −0.7±0.6 NS % ideal-body-weight: I: 85±6/C: 84±13 NS After 6 mo: z-score weight-for-age: I: −1.3±0.8/C: −0.6±0.9 NS % ideal-body-weight: I: 83±6/C: 83±13 NS	Baseline (kcal/day): I: 2400±600 C: 2800±1100 After 3 mo: I: 2700±700 C: 2800±700 NS	Baseline: I: 66±22/ C: 62±25 After 3 mo: I: 60±26/ C: 63±16 NS After 6 mo: I: 62±19/ C: 66±13 NS
Poustie, UK, 2006 [18] Randomised controlled trial (50 patients oral supplementation+dietary counselling (I) vs. 52 patients single dietary counselling (C))	Oral supplement: Oral protein energy supplement Aim of increasing energy intake by 20% of the patients' usual energy intake	Treatment length: 1 y outpatient	N=102 Male=54 Age (y): 2–15 Inclusion criteria: BMI between 0.4 and 25th centile, no weight loss previous 3 mo or 5% weight decrease within 6 mo	Baseline: BMI centile: I: 34.27±23.96/ C: 31.52±25.36 Weight centile: I: 25.07±20.37/ C: 24.69±22.79 Differences after 12 mo: BMI centile: I: 0.67±18.2/ C: −2.32±9.63 NS Weight centile: I: 0.83±10.96/ C: −1.0±7.14 NS	Baseline % RDA: I: 118.43±28.71 C: 116.24±29.59 Differences after 12 mo: I: 24.48±22.87 C: 6.63±25.21 (p=0.01)	Baseline: I: 81.34±16.16/ C: 73.67±18.58 Differences after 12 mo: I: −3.41±13.5/ C: −1.50±14.89 NS

I=intervention group C=control group RDA=recommended daily allowances P-values from original studies added when available ND=not defined NS=not significant

Table 3
Characteristics of enteral tube feeding studies.

First author, country, year study, study design	Type of intervention	Context of intervention	Sample characteristics and inclusion for enteral tube feeding	Results growth parameters	Caloric intake	FEV_1% predicted
Bradley, US, 2012 [22] Retrospective controlled cohort study (20 patients (I) vs. 20 (C))	Overnight feeding, providing 50% of RDA	Follow-up: 1 y (simultaneous with start enteral tube feeding) Home-based Patients enrolled in a 5 y span	N=40 Male: I: 8/C: 8 Mean age (y): I: 9.0±4.4/C: 9.1±4.7 Nutritional status baseline: BMI below 50th percentile	Baseline: z-score weight-for-age: I: −1.40±0.55/C: −1.06±0.74 (p=0.07) z-score BMI: I: −1.19±0.6/ C: 1.10±0.5 (p=0.1) After 6 mo: z-score weight-for-age: I: −0.73±0.79/C: −1.01±0.76 (p<0.001) z-score BMI: I: −0.29±0.84/ C: −1.02±0.67 (p<0.001) After 12 mo: z-score weight-for-age: I: −0.76±0.73/C: −0.86±0.70 (p=0.01) z-score BMI: I: −0.41±0.76/ C: −0.71±0.51 (p=0.07)	ND	Baseline: I (N=14): 76.0±19.5/ C (N=13): 75.7±19.0 (p=0.90) After 6 mo: I: 74.7±22.0/ C: 78.9±24.0 (p=0.46) After 12 mo: I: 74.4±21.4/ C: 82.3±22.9 (p=0.17)
Williams, UK, 1999 [27] Single group Pre-test–post-test (53 patients) Patients acted as their own controls	Overnight feeding, providing 40–60% of RDA	Follow-up: 1 y (simultaneous with start enteral tube feeding) Home-based patients enrolled in a 6 y span	N=53 Male=14 Mean age (y): 22.0±0.8 ≤18 y (N=10; 4 boys): mean age (y): 14.7±0.7 >18 y (N=43; 10 male): mean age (y): 23.7±0.8 Nutritional status: BMI<17 Baseline weight z-score: ND During follow-up 16 patients died	Adults: baseline: weight (kg) 37.4±0.8/z-score BMI: 14.9±0.4 After 6 mo: weight (kg) (N=37): 42.1±1.1 (p=0.0001)/BMI (N=25): 17.7±0.5 (p=0.0001) After 12 mo: weight (kg) (N=22) 44.2±1.3 (p=0.0001)/BMI (N=21): 17.7±0.4 (p=0.0001) Children: baseline: weight (kg) (N=10) 31.9±2.7 After 6 mo: weight (kg) (N=9): 35.3±3.3 (p<0.02) After 12 mo: weight (kg) (N=6) 35.1±4.7 (p<0.02)	ND	Baseline: 21 (13–35) After 6 mo: 20 (13–35) After 12 mo: 22 (10–40) NS
Truby, Australia, 2009 [25] Single group Pre-test–post-test (14 patients) Patients acted as their own controls	Overnight feeding 5–7 days/week, providing 1/3–1/2 of estimated energy requirements	Follow-up: 2 y (simultaneous with start enteral tube feeding) Home-based Patients enrolled in a 6 y span	N=14 M=7 Age (y): 0.42–13 Mean age (y): 6.63	Baseline: z-score weight-for-age: −1.20±0.82/BMI (N=9): −1.13±0.61 After 1 y: z-score weight-for-age: −1.05±0.73 (p=0.475)/BMI (N=9): −0.56±0.62 (p=0.01) After 2 y: z-score weight-for-age: −1.15±0.92 (p=0.546)/BMI (N=9): −0.98±1.01 (p=0.108)	ND	Baseline: (N=7) 71.02±13.53 After 1 y: 67.26±17.54 (p=0.405) After 2 y: 66.28±14.73 (p=0.498)
Van Biervliet, Belgium 2004 [26] Single group Pre-test–post-test (11 patients) Patients acted as their own controls	Overnight feeding, providing 40% of RDA	Follow-up: 2 y (simultaneous with start enteral tube feeding) Home-based	N=11 Male=3 Age (y): 0.6–14.8 Median age (y): 9.4 Nutritional status: weight-for-height<85% or z-score height<−2	Baseline % weight-for-height: median: 81 (67–90)/z-score BMI: −2.34 (−2.95–−1.29) After 3 mo (N=7): % weight-for-height: >90/z-score BMI −1.11 (−2.18–1.35) After 6 mo (N=7): % weight-for-height: 91 (75–119) (p≤0.05)/z-score BMI: −1.32 (−2.04–0.63) (p≤0.05)	Kcal/day before insertion gastrostomy 940–2011 After start enteral tube feeding: 1027–2666 RDA by enteral tube feeding: 40% (14%–90%)	NS
Efrati, Israel, 2006 [23] Single group Pre-test–post-test (21 patients)	Overnight feeding, providing 40–60% of RDA	Follow-up: 2 y (simultaneous with start enteral tube feeding) Home-based Patients enrolled in a 9 y span	N=21 Male=10 Age: 8 mo–20 y Mean age: ND	Baseline: z-score weight-for-age: −3.1±1.4/z-score BMI: −2.1±1.3/% ideal-body-weight: 84.6±8.5 After 6–12 mo (N=21): z-score	ND	Baseline: (N=16) 44.2±13.9 (25–77) After 6–12 mo: (N=15): 41±13.3

Patients acted as their own controls			Nutritional status: % weight-for-height below 85 or weight loss for more than three consecutive mo During follow-up 1 patient died	weight-for-age: −2.5±1.5 (p=0.013)/z-score BMI: −1.2±1.2 (p=0.001)/ % ideal-body-weight: 95.1±12.9 ND After 18–24 mo (N=14): z-score weight-for-age −2.6±1.5 (p=0.026)/z-score BMI: −1.27±1.11 (p=0.006)/ % ideal-body-weight: 96.5±11.1 (p=0.003)		(25–67) (p=0.05) After 18–24 mo: (N=14) 41.4±16.1 (16–65) trend toward improvement
Rosenfeld, US, 1999 [24] Single group Pre-test–post-test (21 patients) Patients acted as their own controls	Overnight feeding, providing 1/4–1/2 of RDA	Follow-up: 4 y (simultaneous with start enteral tube feeding) Home-based Patients enrolled in a 13 y span	N=21 Male=7 Age (y): 1.1–20.8 Median age (y): 7.4 Weight less than 90% of ideal, linear stunting or failure to progress along baseline weight percentile for 3 to 6 mo	Baseline (N=21): median % ideal-body-weight: 89 (72–95)/median weight: 2nd percentile (0.2–36) After 6–18 mo (N=18): median % ideal-body-weight: 90 (85–99) (p≤0.002)/median weight: 12th percentile (1–28) (p≤0.002) After 18–30 mo (N=18): median % ideal-body-weight: 93 (86–98) (p≤0.002)/median weight: 12th percentile (1–29) (p≤0.002) After 30–48 mo (N=14): median % ideal-body-weight: 98 (94–107) (p=0.002)/median weight: 19th percentile (1–31) (p=0.002)	ND	ND
Best, US, 2011 [28] Single group Pre-test–post-test (46 patients) Patients acted as their own controls	ND	Follow-up: 4 y (2 y pre-treatment–4 y post-treatment) Home-based Patients enrolled in a 20 y span	N=46 Male=28 Age (y): 5–50 Age at gastrostomy tube placement <18 y: (N=33; 20 boys) mean age (y): 11 (5–15) ≥18 y: (N=13; 8 men) mean age (y): 26 (18–50) Nutritional status baseline: Overall: BMI percentile: 13.3 <18 y: ND ≥18 y: BMI absolute: 18.2 During follow-up 4 patients died, 8 underwent lung transplantation	BMI percentile 2 y pre-treatment–1 y post-treatment Overall (N=46): from 13.3 to 19.1, median % BMI change: +6.3% (p=0.0007) Men (N=8): median % BMI change: +4.6% (7 patients improved) Women (N=5): median % BMI change: −8.3% (1 patient improved) Boys (N=20): median % BMI change: +8.3% (16 patients improved) Girls (N=13): median % BMI change: +7.1% (12 patients improved) BMI percentile 2 y pre-treatment–2 y post-treatment Overall (N=39): from 14.6 to 36.8, median % BMI change: +13.3% (p<0.0001) Men (N=5): median % BMI change: +9.0% (5 patients improved) Women (N=3): median % BMI change: −5.0% (1 patient improved) Boys (N=19): median % BMI change: +14.0% (15 patients improved) Girls (N=12): median % BMI change: +16.0% (10 patients improved) BMI percentile 2 y pre-treatment–4 y post-treatment Overall (N=29): from 14.5 to 26.0, median	ND	Slope before start enteral tube feeding per year Men: −5.91 (p=0.0019) Woman: − 8.59 y (p=0.0001) Boys: −1.13 (p=0.3453) Girls: −4.32 (p=0.0055) Slope change after start enteral tube feeding per year Men: 5.01 (p=0.0159) Woman: 4.48 (p=0.0712) Boys: 1.49 (p=0.2297) Girls: 4.02 (p=0.0107)

(continued on next page)

Table 3 (*continued*)

First author, country, year study, study design	Type of intervention	Context of intervention	Sample characteristics and inclusion for enteral tube feeding	Results growth parameters	Caloric intake	FEV_1% predicted
				% BMI change: +8.9% (p=0.0067) Men (N=3): median % BMI change: +13.5% (3 patients improved) Women (N=1): median % BMI change: −20.7% (0 patients improved) Boys (N=15): median % BMI change: +6.8% (8 patients improved) Girls (N=10): median % BMI change: +14.1% (8 patients improved)		
I=intervention group	C=control group	RDA=recommended daily allowances		P-values from original studies added when available	ND=not defined	NS=not significant

studies, the treatment length varied from 8 weeks [19] to 1 year [18]. In both, the follow-up started simultaneous with the introduction of the oral supplement and the duration was equal to the treatment length. The two other oral supplementation studies both had a treatment and follow-up period of 3 months [17,20] respectively. The follow-up of the enteral tube feeding interventions started simultaneous with the start of the tube feeding and lasted up to 4 years [24,28]. The control groups were CF patients who did not have the intervention [11–18,20,22], or subjects who served as their own control [12,19,23–28]. Data are summarized in Tables 1, 2 and 3, respectively.

Sample characteristics of the nutritional intervention studies tended to be heterogeneous. The sample sizes varied from 7 [13] to 102 subjects [18], and age ranged from 5 months [25] to 50 years [28]. Furthermore, the baseline nutritional status differed from well-nourished adult patients (BMI 21.0) [16] to severely malnourished paediatric patients (mean z-score weight-for-age −3.05) [23].

The primary outcome was weight gain. Changes in caloric intake per day and/or the FEV_1% pred. were described in 9 [11–14,17–20,26] and 11 studies respectively [14–18,20,22,23,25,27,28].

3.1. Behavioural intervention studies

3.1.1. Design

Six behavioural intervention studies were included which differed in design [11–16]. The 'home-based' nutritional education programme of Watson et al. focusing on well-nourished adults, was unique [16]. In this study, the intervention group received 10 learning modules which were designed to take 30 min per week and were to be completed at home. They also received a newsletter every 2 weeks and 3 workshops at the clinic were organised as well: before, halfway and at the end of the home-based programme. The intervention group was rewarded for making changes as well as for strengthening their behavioural changes. The control group received standard care. The follow-up measurements of anthropometry and pulmonary function took place 6 and 12 months after the end of the intervention. The other five studies focused on behavioural modification in children who in general had z-scores for weight indexes below 0 and above −1. The first behavioural and nutritional intervention in the study of Powers et al. was conducted over a 1 year period in which families received 8 one-hour sessions which included nutritional counselling and behavioural management training [11]. This relatively small study (8 patients) served as pilot for a subsequent study conducted in 2005 [12]. In the latter, parents were trained in effective child behavioural management skills, combined with individualized nutritional counselling that targeted increasing energy intake in one specific meal each week. The study was performed over an 8 week period and included a baseline study visit and 6 intervention sessions held in week 3 to 8. After these 8 weeks, the control group was able to cross over to the same intervention as given to the first intervention group to replicate the effect of the intervention. The one-year follow-up assessments for anthropometric data took place every 3 months and a diet diary was completed at 3 and 12 months follow-up.

In all 3 studies of Stark et al., both the parents and children in the intervention and control group were provided with the same nutritional information and caloric goals during 7 weekly sessions [13–15]. In the first 2 studies performed by Stark et al. [13,14], parents of the intervention group were instructed in behavioural management to motivate their child to eat, while the children received behavioural training in meeting weekly caloric goals as well as a behavioural reward programme. In the 2011 study [15] the intervention group consisted of the intervention group and the control group of the previous study of Stark et al. conducted in 2009 [14]. This implied that the intervention group received either behavioural management instructions and nutritional counselling or nutritional counselling only. Pooling of both groups from the 2009 study into the 2011 intervention group was considered correct as no significant differences at 2 year follow-up were found between these 2 groups. Growth in the combined intervention group was compared with growth of CF patients receiving standard care during the same time period. This control group was randomly drawn from the US-CF registry. In all 3 studies the follow-up assessments for anthropometric, caloric intake and pulmonary function data took place at 6, 12 and 24 months and in both the 2009 and 2011 studies also at 3 and 18 month after the end of treatment.

3.1.2. Nutritional status

Watson et al. and Powers et al. 2003 described no effects of the behavioural intervention on nutritional status [11,16]. The intervention group in the study of Powers et al. 2005 had normal weight velocities [12] but no information was available on the control group because this group crossed over to the combined intervention group. Both the 2003 and 2009 studies of Stark et al. reported that the intervention group had gained more weight in comparison to the control group at initial evaluation points [13,14]. However after 2 years follow-up the intervention group had not gained more weight than the control group. The 2011 study of Stark et al. demonstrated a significant less decline in BMI z-score between the combined intervention group and the control group that was randomly selected from the US-CF registry [15].

3.1.3. Caloric intake

Four behavioural studies described the caloric intake per day [11–15]. In the pilot study of Powers et al. 2003, no significant differences were found in the caloric intake between the intervention group (behavioural intervention combined with nutritional counselling) and the control group (nutritional counselling only) [11]. Nonetheless in 2005 the same group found a significant improvement in caloric intake after 3 months as well as after 12 months in a group that received behavioural and nutritional counselling [12]. Similar results were found in the group who crossed over from the control group to the intervention group. In 2 studies of Stark et al., children receiving behavioural intervention combined with nutritional counselling increased their daily caloric intake more

than children who received nutritional counselling only [13,14], although this effect did not persist after a 2 year follow-up [14].

3.1.4. Pulmonary function

Three behavioural studies described pulmonary function before and after the intervention [14–16]. No significant differences in pulmonary function were found before and after intervention, although in one study the decline in pulmonary function in the intervention group seemed to be slower than in the control group, although not significantly so [15].

3.2. Oral supplementation studies

3.2.1. Design

Included were 4 studies which investigated the effect of adding high energy supplements to the usual oral intake in patients with weight indexes z-scores below 0 and above −2 [17–20] of which the children in the study of Poustie et al. [18] and Skypala et al. [19] had weight indexes above z-score −1. The supplement in each study was different, but aimed at either increasing energy intake by 20% or having an intake that was at least equivalent to the calculated energy requirements. In the study of Skypala et al. the children and adults acted as their own controls [19]. In the 4 weeks pre-treatment period they were monitored on their usual diet including oral supplements and overnight enteral tube feeds. In the 8 weeks intervention period, the overnight enteral tube feeds where continued while the oral supplements were replaced by the intervention supplement which was prescribed in a dose equivalent to a minimum of 20% of the patients' pre-trial energy intake. The intervention supplement was a flavoured powder which was not fortified which vitamins and minerals and, when reconstituted with 240 ml of full-fat milk, contained 2 kcal/ml. The anthropometric assessments took place during the intervention at week 0, 4 and 12. No further follow-up measurements were performed.

The children enrolled in the study of Steinkamp et al. were randomly allocated to a control group or to an intervention group [20]. During 3 months both the control group and the intervention group received dietary counselling while the intervention group additionally received an oral supplement with 1.0 kcal/ml with 31% of energy from fat (half of which was linoleic acid), and 16% of energy from protein. Anthropometric, caloric and pulmonary function data were obtained after 3 months follow-up. In the relative small study (13 patients) of Kalnins et al., a ready-to-use supplement with 1.5 kcal/ml, consisting of 30% of energy from fat and 20% of energy from protein was prescribed to children and adults, during a 3 months period with the aim to increase energy-intake by 20% of predicted energy needs [17]. The control group received dietary counselling in which it was advised to increase the energy intake by eating high calorie foods. Anthropometry and pulmonary function were evaluated at the end of the intervention and after 3 months follow-up, the change in caloric intake only at the conclusion. In the one-year study of Poustie et al., children were randomised into a group who had dietary counselling and oral supplements and into a group who had dietary counselling only [18]. The nutritional facts of the prescribed oral supplements were heterogeneous but all aimed at increasing the energy intake by 20%. The assessments for anthropometric, caloric intake and pulmonary function data took place during the intervention at 3, 6 and 12 months.

3.2.2. Nutritional status

Two studies described a significant weight gain after intervention, either when comparing to the pre-intervention weight in the same group [19] or when compared to the weight of a control group without the intervention [20]. The other 2 studies did not find an effect on weight variables at the end of the intervention period [17,18].

3.2.3. Caloric intake

All 4 studies described the caloric intake. Apart from the study by Kalnins et al. [17] all showed a significant increase in caloric intake at the end of the intervention period [18–20].

3.2.4. Pulmonary function

Three studies described the pulmonary function and in none of these studies significant differences in FEV_1% pred. were found between intervention and control groups, neither before nor after the intervention [17,18,20].

3.3. Enteral tube feeding studies

3.3.1. Design

Seven studies on enteral tube feeding were included [22–28]. Four studies enrolled patients with weight indexes z-scores below −1 [22,24,25,28], and 3 studies included malnourished patients (weight indexes z-scores below −2) [23,26,27]. Each investigated the effect of overnight tube feeding given by gastrostomy, thus providing 25%–60% of the recommended daily advised (RDA) caloric intake. The study of Bradley et al. [22] was unique as it was a pair-matched controlled study, while all other studies did not include a control group, but evaluated the effect of the intervention by comparing baseline weight indexes with the same variable after enteral tube feeding was implemented for some time. Bradley et al. supplemented 18 children, who were enrolled over a 5-year span, with a whole-protein formula, 1 with a partially hydrolysed formula and 1 with an elemental formula. The anthropometric and pulmonary assessments took place at 6 and 12 months. Williams et al. enrolled both children and adults and prescribed a concentrated modular elemental feed combined with Polycose (up to 2.6 kcal/ml) to pancreatic insufficient patients and to sufficient patients a whole protein feeding (1.5 kcal/ml) [27]. For both groups the enteral tube feeding provided 40–60% of the RDA and at month 6 and 12 anthropometry and pulmonary function data were obtained. In the study of Truby et al., children were provided with enteral tube feeding containing 1 or 1.5 kcal/ml. Anthropometric and pulmonary function data were assessed 1 and 2 years after the start of the enteral tube feeding [25]. Both studies enrolled patients over a period of 6 years. The

children in the study of Van Biervliet et al. received 40% of the RDA by providing a high energy (1.5 kcal/ml) polymeric tube feed [26]. They studied data of children from 2 years before and after the gastrostomy insertion and evaluation of anthropometric data took place after 3 and 6 months of the gastrostomy insertion. The time span of enrolment was not described. Efrati et al., Rosenfeld et al. and Best et al. investigated the effect of enteral tube feeding of both children and adults included over a period of respectively 9-years, 13-years and 20-years [23,24,28]. The follow-up assessments for anthropometric data in the study of Efrati et al. took place after 6–12 months and 18–24 months while the other 2 studies assessed both anthropometric and pulmonary function data in various time periods during the 4 years of follow-up [24,28]. These last 3 studies did not mention the type of the enteral tube feeding prescribed.

3.3.2. Nutritional status

In the only study that included a control group, the intervention group significantly improved in z-score weight and z-score BMI after 6 and 12 months of enteral tube feeding [22]. Apart from the study by Williams et al. [27] who reported both absolute weight gain and z-score BMI, the other studies reported either percentiles, percentages or z-scores for weight variables. Also those studies that included both children and adults [23,24,27,28] reported separate data for adults and children.

In 5 studies, a significant improvement in the weight variables was found after the start of enteral tube feeding, with follow-up periods lasting from 1 year [26,27] to 2 years [23] to 4 years [24,28]. Although, Truby et al. described a significant improvement in z-score weight after 1 year of enteral tube feeding, in the second year the weight gains were less evident with no significant change in the weight indexes [25].

3.3.3. Caloric intake

The caloric intake was only reported in the study of Van Biervliet et al. [26]. In this study, patients improved their caloric intake with approximately 40% of the recommended daily intake after the start of the enteral tube feeding.

3.3.4. Pulmonary function

Five studies described the pulmonary function [22,23,25,27,28]. Stabilisation in pulmonary function in the intervention group after 6 and 12 months providing enteral tube feeding was found in the studies of Bradley et al. [27] and Williams et al. [22]. Two studies demonstrated a gradual decline in pulmonary function, respectively from 71% FEV_1 pred. at baseline to 67% after 1 year and to 66% after 2 years of gastrostomy feeding [25], and from 44% at baseline to 41% FEV_1 pred. after 1 year of gastrostomy feeding, and stabilising at 41% FEV_1 pred. after 2 years [23]. Best et al. found a significant reduction in the rate of pulmonary decline after the start of enteral tube feeding in girls, as well as in adult men (all $p<0.05$), while women showed a trend toward improvement [28]. For boys, no significant improvement in the decline of pulmonary function was found, but it should be noted that the initial rate of pulmonary function decline in boys was already low (−1.13%/y) in contrast to the initial rates of decline in other subgroups (from −4.32%/y to −8.59%/y), so an improvement might be more difficult to detect.

4. Discussion

This review demonstrates that in 1 out of the 6 behavioural studies a significant weight gain was found and in another study an increased caloric intake, although this was not reflected in weight gain. Oral supplementation proved to be successful in improving weight variables in 2 out of 4 studies, and in caloric intake in 3 out of 4 studies No positive effects of behavioural interventions or oral supplementation on pulmonary function were described. In all studies, enteral tube feeding via gastrostomy results in significant weight gain and also slows a further decline in pulmonary function in patients with CF.

The earlier meta-analyses by Jelalian et al. [8] in 1997, included 4 behavioural, 6 oral supplementation, 5 enteral tube feeding and 3 parental nutrition studies reported that all interventions were effective in inducing weight gain, with parenteral nutrition having the largest effect, then enteral nutrition, then oral supplementation while behavioural interventions had the smallest effect. However the difference in weight gain between the four types of intervention was not significant. As opposed to this earlier study, the current study did not find an improvement in weight for each nutritional intervention. This difference might be partly due to the small sample size for the studies analysed by Jelalian, which ranged from 3 to 15 patients, with a total number of 17 patients analysed for behavioural intervention, 56 for oral supplementation and 52 for enteral nutrition, which is less than the largest single centre study in each of these three groups in the current review. Moreover, the results of the meta-analysis represented only the effectiveness of half of the studies conducted because other studies were lacking data for an effect size calculation. The limited number of available studies could significantly affect the estimated effectiveness and possible studies which were not effective in improving weight gain were excluded. Given the differences in sample size numbers and limited data analysed, it is conceivable that some of the findings by Jelalian et al. could not be replicated in the current review. In addition the nutritional status for the CF population at large has been considerably improved since the meta-analysis by Jelalian was done, with, for example, a 7.8% gain in median BMI percentile between 2000 and 2010 [9]. In the current population of CF patients, with a better nutritional status, the effect of interventions which induce only marginal weight gain would be harder to detect, especially conducted in patients who are only just below z-score 0 with respect to weight variables, such as in the behavioural intervention studies now analysed.

The generalizability of the results of studies analysed in this review was limited due to the heterogeneity of the intervention groups, with respect to age, nutritional status, caloric intake, pulmonary function and the duration of the studies. Firstly, the sample size varied widely, from 7 [13] to 102 patients [18],

while 6 out of 17 studies reviewed (respectively 3 behavioural [11–15], 1 oral supplementation [17] and 2 enteral tube feeding interventions [25,26]) included less than 15 patients. Secondly, the patients included in the reviewed studies had a large age range, varying from 5 months [25] to 50 years [28], with nutritional intervention studies in children being overrepresented as respectively 10 (5 behavioural [11–15], 2 oral supplemental [18,20] and 3 enteral tube feeding interventions [22,25,26]) and 6 (2 oral supplemental [17,19] and 4 tube feeding interventions [23,24,27,28]) out of 17 studies analysed enrolled children or both children and adults while 1 study (behavioural intervention [16]) included only adults. Although none of the studies demonstrated that specific age groups benefit from a particular intervention, the impact of age on treatment efficacy is not clear at present. Thirdly, the included patients varied in baseline weight from well-nourished [16] to malnourished [23,26,27]. Behavioural interventions were mainly conducted in patients with weight indexes above z-scores −1 [11,12,14–16] while enteral tube feeding interventions were only done in patients with weight indexes below z-scores −1. Moreover malnourished patients (weight indexes below z-scores −2) received only enteral tube feeding and no other type of intervention [23,26,27]. Therefore the effectiveness of behavioural interventions and/or oral supplementation in malnourished patients cannot be reviewed. Fourthly, respectively 8 [15,16,22–25,27,28] and 6 studies [11–13,19,24,26] lacked data on caloric intake or pulmonary function so the effect of the interventions on these variables could not be assessed consistently. Lastly, the study duration varied from 7 weeks in behavioural interventions [13–15] to 4 years in enteral tube feeding [24,28] and the follow-up from 8 weeks in oral supplementation [19] to 4 years in enteral tube feeding studies [24,28].

It is also important to note that a single research group from the Cincinnati Children's Hospital Medical Centre, was responsible for 5 out of 6 behavioural intervention studies [11–15]; no independent confirmation of their results has been published so far. So the generalizability of their results is unclear at present. In addition the intervention group enrolled in the study of Stark et al. 2011 [15], was the study group and control group from the study of Stark et al. 2009 [14], which approach was considered justified as no differences between both groups were found at final follow-up. The results of this combined intervention group were subsequently compared to a nationwide reference group randomly drawn from the US-CF registry. This registry stored patient information from all centres, including non-specialized centres. However patients from centres with a focus on CF care often show better growth results than nationwide cohorts [3,29], so it is unclear as to whether the better growth described by Stark et al. for the intervention group is not – partly – due to this effect.

Despite these limitations, some conclusions seem to emerge from the studies reviewed. Nutritional intervention seems especially effective when applied to severely malnourished patients (weight indexes z-scores below −2); in this patient group enteral tube feeding, which is usually or most often done through a gastrostomy in any patient needing this intervention for a longer period, has proven to be successful, both to improve nutritional status and to slow decline in pulmonary function [21,23,25]. The studies included in this systematic review give less guidance for patients with weight indexes z-scores below −1 and above −2. In those patients enteral nutrition is also effective, at least during the first year [20,22,24,26]. As this intervention is invasive, oral supplementation might be started initially, as the study of Steinkamp et al., conducted in patients with weight indexes below −1 and above −2, demonstrated both a significant weight improvement and an increase in caloric intake [20]. With respect to behavioural intervention in this patient group only the 2003 study by Stark et al. showed a trend in weight gain during the first year, but not at the end of the follow-up [13]. So it is not clear at present as to whether CF patients with z-scores for weight indexes below −1 and above −2 benefit from this intervention. In patients with weight indexes z-scores below 0 and above −1 as enrolled in the studies of Skypala et al. [19] and Poustie et al. [18], the addition of oral supplementation seems successful in improving weight [19] and/or increasing the caloric intake [18]. Only one behavioural intervention conducted in this patient group (Stark et al. 2009 [14]) showed significant weight gain, but only at the end of the intervention, and not at final follow-up; in addition, one behavioural study (Powers et al. 2005 [12]) described an increased caloric intake. So, to date it is unclear as to whether this intervention should be routinely implemented in CF patients with a less than normal weight.

Nowadays, the nutritional support is an integral part of multidisciplinary care of patients with CF, supported by international clinical guidelines for nutritional management [6,7]. These guidelines provide recommendations for identifying patients at-risk for malnutrition as well as for those with actual malnutrition. In these groups early intervention is extremely important to prevent negative long-term effects, although it is not always clear at present which type of intervention is most appropriate. Future studies, which should include a control group receiving current best treatment [6,7] might determine more precisely which patient group may benefit most from behavioural interventions and/or oral supplements. The behavioural and oral supplementation interventions described in this systematic review also were relatively short (maximally 1 year, mostly 3 months or less). As the aim for CF patients is to obtain a — near – normal nutritional status for their entire life time, future studies should have a longer intervention and follow-up, so it will become clear whether observed short term effects will persist over a longer period. Finally, as the ultimate goal for CF patients is a slower decline of pulmonary function, studies investigating nutritional interventions should include pulmonary function variables. Ideally these goals would be attained in prospective randomised controlled trials designed to assess the effect of a behavioural or oral supplementation intervention in CF patients with a weight for age z-score between 0 and −2, as for these interventions the effect is not sufficiently clear yet. Study duration should be at least one year, as is the follow-up, and outcome variables should include weight variables as well as FEV_1% pred.

5. Conclusion

The studies included in this systematic review give less guidance for the role of behavioural intervention and oral supplements. However it can be concluded that enteral tube feeding is effective to improve the nutritional status, especially in malnourished patients, and to slow further pulmonary function decline in patients with Cystic Fibrosis.

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