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**Title:** Evaluating the impact of 2006 Australasian Clinical Practice Guidelines for Nutrition in children with cystic fibrosis in Australia

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**Abstract**

Objectives: To determine the association between the implementation of the 2006 Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis (CF) and the nutritional status of children participating in the Australian Cystic Fibrosis Data Registry (ACFDR).

Methods: This research consisted of a quantitative study using ACFDR data and a survey of clinicians and dietitians treating children with CF. Two independent cohorts of children (2-5 years and 6-11 years) were selected from ACFDR between 1998-2014 (N = 2,304). Generalised estimating equation model was used to assess weight, height and body mass index (BMI) *z-scores* for each patient before and after the implementation of the nutrition guidelines. A nationwide online survey was sent to 48 clinicians to explore the enablers and barriers to implementation of the guidelines.

Results: Data analysis showed significant increase ($p<0.05$) in mean weight, height and BMI *z-scores* ranging from 0.06 to 0.18 after implementation of the guidelines in both cohorts of children. Nineteen (39%) clinicians participated in the survey. The majority of the respondents adopted the recommendations into their practice and used the guidelines as part of their professional development. Structural barriers included a lack of adequate staff resources and clinic space for consultations, inappropriate staff classification, high staff turnover and lack of mentoring support.

Conclusion: In children participating in the ACFDR, nutritional status improved after the implementation of the 2006 guidelines. Survey results revealed enablers and barriers to guideline implementation and will inform implementation strategies for the revised Australasian nutrition guidelines for CF, released in 2017.

**Keywords:** cystic fibrosis, guidelines, nutrition, registry

## Introduction

Cystic Fibrosis (CF) is a common, genetically acquired, life-shortening chronic illness affecting primarily the lungs and digestive system due to a malfunction in the exocrine system, responsible for producing saliva, sweat, tears and mucus [1]. More than 30,000 people with CF live in the USA and approximately 3,300 in Australia [2, 3].

Manifestations of the disease often include frequent respiratory infections resulting in progressive scaring of lung tissues and impaired absorption of nutrients resulting in suboptimal weight gain and growth [4]. Both malnutrition and poor lung function are associated with an increased risk of mortality, therefore, treatments and interventions in patients with CF need to aim at maintaining good nutrition and preserving lung function [5-7]. Despite recent advances in management of the disease, poor nutrition remains common due to increased resting energy expenditure, malabsorption and reduced energy intake [4, 8, 9]. Nutritional status and pulmonary function are closely linked and stunting has been found to be an independent predictor of mortality in patients with CF [10, 11]. Good nutrition in early life is particularly important due to rapid physical and cognitive development. Despite improvements, associated with centre-based care, high energy unrestricted fat diets, pancreatic enzyme replacement therapy and newborn screening [12-15], the problems of growth failure and poor nutritional status remain a challenge [10, 15, 16].

In Australia, following a survey of dietetic practice and management of CF in 2006 [6], the Dietitian Association of Australia published the 2006 Australasian Clinical Practice Guidelines for Nutrition in CF [17]. The guidelines aimed to reduce variations in practice and improve the nutritional status and quality of life of patients with CF and their families [6, 17]. The guidelines made recommendations regarding dietetic staffing levels, nutritional assessment, nutritional requirements, pancreatic enzyme replacement therapy and nutritional

support as well as managing complications including pancreatitis and CF related diabetes, and special situations including pregnancy and nutrition for lung transplantation. These guidelines were distributed to dietitians and other health professionals working in specialist CF clinics. They also were published on the websites of professional associations. In addition, workshops for dietitians working in specialist CF clinics were held at the Annual Meetings of the Dietitians Association of Australia CF Special Interest Group during 2007.

Recently, evidence-informed and practice based guidelines on the nutritional care of infants, children and adults with CF have been established including those by the ESPEN-European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)-ECFS [9], as well as the Cystic Fibrosis Foundation (CFF) guidelines on enteral tube feeding both published in 2016 [18].

To describe trends and patterns of growth and pulmonary function in people with CF, and to examine longitudinal associations amongst these variables, a rich data source is needed. To collect such information, CF patient registries have been established in the USA, United Kingdom, Europe, Australia and New Zealand [19]. The Australian Cystic Fibrosis Data Registry (ACFDR) is a national registry that was established in 1998, and collects clinical data on patients with CF attending specialist clinics. It captures >90% CF patients enrolled in the registry [20, 21], and at the end of 2015 the ACFDR held records of 3,379 Australians diagnosed with CF [2].

The aim of this study was to determine the association between the implementation of the 2006 Australasian Clinical Practice Guidelines for Nutrition in CF and the nutritional status of children participating in the ACFDR between 1998-2014.

## Material and methods

*Study design*

This quantitative study consisted of two components: 1) analysis of registry data of children enrolled in the ACFDR, and 2) survey of clinicians treating children with CF in Australia.

*ACFDR data*

The ACFDR contains detailed demographic and clinical information of patients with a confirmed diagnosis of CF, receiving clinical care at twenty-three accredited CF centres in Australia (2, 20). Currently there are ten paediatric specialist CF centres participating in the ACFDR. On a regular basis, for each patient the registry collects data regarding lung function, nutrition, mutation, respiratory microbiology, hospitalisation and treatment. The registry provides detailed annual and centre-specific reports, distributed to the clinicians in the participating sites. A detailed description of the registry is described elsewhere [2, 21].

In this study, nutritional data of children from two independent cohorts, 2-5 and 6-11 years of age, were collected longitudinally from 1998 to 2014. We have chosen two different age cohorts due to differences in rates of normal growth, eating behaviour and development of children between these two groups. This choice was based on the Centres for Disease Control and Prevention Growth Charts [22].

*Survey*

A simple ten-question anonymous survey was conducted among medical staff (paediatric consultants and fellows in respiratory/thoracic medicine and registrars in an accredited respiratory medicine program) and dietitians across Australian paediatric specialist CF centres aiming to explore enablers and barriers to the implementation of the 2006 nutrition guidelines at their centres. Doctors were identified through their centre's involvement in the ACFDR and dietitians were identified through the Dietitians Association of Australia CF Interest Group network.

The survey was based on the theoretical domains framework [23] to examine current practice and identify enablers and barriers associated with the implementation of the guidelines. The survey consisted of the following four components: 1) demographic characteristics of participants, 2) implementation of the guidelines, 3) guideline recommendations, and 4) evidence for the guidelines. A survey was delivered online via Qualtrics Survey Software [24] between August 2017 and February 2018.

*Outcome measures*

Nutritional parameters analysed in this study were weight, height and body mass index (BMI) function measurements *(z-scores)* obtained on the occasion of the best lung function annually. *Z-scores* represent child's or adolescent's weight, height or BMI relative to the distribution of weights/heights/BMI observed in a normal reference population of children and adolescents of the same sex and age, transformed onto a standardised scale representing the signed distances from the population mean divided by the standard deviation. These scores are compiled for children and adolescents aged from 2 to less than 18 years using the tables published by Centres for Disease Control and Prevention [25].

*Confounding factors*

Age, sex, pancreatic status, dornase alfa (*Pulmozyme*) therapy, number of ever-colonised positive sample of *Pseudomonas aeruginosa* and presence of a G551D mutation were considered as potential confounders in this study.

Dornase alfa (*Pulmozyme*) was included to the analysis as a possible confounder because of its mucolytic therapy use, which might be an indication of a more severe lung disease and could potentially result in poorer nutritional outcomes in children undertaking this therapy [26]. Dornase alfa (*Pulmozyme*) was listed on the Australian Pharmaceutical Benefits Scheme in 1996 and recommended for children age of six years or older [27]. In 2009 the listing was

extended to those under five years of age with more severe lung disease. Compared to the USA, the lower rate of dornase alfa (*Pulmozyme*) use in Australia was likely to be due to strict qualification criteria for government subsidisation of this expensive medication, which in 2003 limited ongoing use to those who had demonstrated an improvement in lung function of at least 10% within a month of initiating treatment [28].

Another major factor associated with increased morbidity and mortality and, therefore, poorer nutritional outcomes in CF patients is chronic *Pseudomonas aeruginosa* infection [29, 30]. Starting from the late 1990s, eradication treatment for *Pseudomonas aeruginosa*, to prevent or delay chronic infection, became more widely adopted [31] with the process formally recognised in the 2008 CF Standards of Care in Australia [32]. We accounted for the possible influence of improved treatment and medication in our analysis via adjusting for the number of ever-positive *Pseudomonas aeruginosa* results recorded in the registry.

Recent studies have shown that the use of CF transmembrane conductance regulator (CFTR) modulator *ivacaftor* in responsive gating mutations, improves the nutritional outcomes of CF patients [33-35]. Widespread use of *ivacaftor* in Australia did not occur until 2014 after approval by the Therapeutic Goods Association for use in children of six years of age and more with G551D mutation (https://www.tga.gov.au/auspar/auspar-ivacaftor). A small number of children also had access to the treatment in Phase III clinical trials conducted between 2009 and 2011; however, the exact number of patients is not known, as this was not recorded in the registry [36, 37]. In 2015, 6.4% of the total CF population had the G551D mutation [2]. Despite low numbers of exposure to *ivacaftor* in the study sample, there is a possibility of a substantial change in nutrition amongst those receiving this treatment. Since the ACFDR commenced collecting the *ivacaftor* data in 2016, the gating mutation G551D was used as a proxy for exposure to *ivacaftor* in the analysis.

*Statistical analyses*

ACFDR data

Descriptive statistics were used to describe the study population and nutritional outcomes in children with CF before and after the implementation of the 2006 guidelines. Generalized estimating equations (GEE) models were employed to examine the associations between the nutritional status and introduction of the guidelines in 2006. GEE modelling is appropriate for analysis of the longitudinal data, as it is used to estimate the parameters of a generalized linear model with a possible unknown correlation between outcomes and it could be interpreted in a similar way to linear regression [38]. Because the outcomes of the model are continuous, a Gaussian distribution for the family of distributions was specified, along with an identity link function for the model and the exchangeable correlation matrix.

Two GEE models, one unadjusted, and another adjusted for age, sex, pancreatic status, use of dornase alfa (*Pulmozyme*), a number of ever-colonised positive *Pseudomonas aeruginosa* and G551D mutation were designed to compare nutritional outcomes in children 2-5 and 6-11 years of age. Comparisons were made between two periods for each group: 1998-2006 (before the implementation of the 2006 nutrition guidelines) and 2007-2014 (after the implementation of the 2006 nutrition guidelines).

For all analyses in this study, level of significance was set to 5%.

Data analysis was conducted in Stata 15.0 (StataCorp, College Stationb, TX, USA).

Survey data

All survey responses were anonymous and managed using a simple numerical identifier. Descriptive statistics were reported as frequencies in each response category, or means (SD) for continuous type of the data that were collected in a Likert scale.

*Ethics approval*

Collection analysis of the data for this study were approved by the Human Research Ethics Committee (RES-17-0000-384L) at Monash Health, Melbourne, Victoria. Institutional ethics committee approval was obtained from the participating ACFDR sites providing paediatric care and the approaches made to clinicians to participate in the survey.

**Results**

*ACFDR data*

The study sample of 2,304 children with CF aged 2-5 and 6-11 in any of the years from 1998 to 2014 was extracted from the ACFDR. This resulted in a total of 18,261 annual records with clinical measurements over the study period in 1998-2014, of which 4,146 (30.8%) and 3,595 (74.5%) for children 2-5 and 6-11 years of age respectively were recorded prior to the implementation of the nutrition guidelines in 2006 (Table1).

[Table 1 about here please]

Of the records obtained from children 2-5 years of age, more than seven percent had one or more copies of the G551D mutation, 85.2% of records indicated pancreatic insufficiency, 25.3% of the records identified the use of dornase alfa, and 35.9% had at least one record of positive *Pseudomonas aeruginosa*. Of the records obtained from children 6-11years of age, six percent had one or more copies of the G551D mutation, 78.1% indicated pancreatic insufficiency, 36.5% identified the use of dornase alfa and 31.7% had at least one record of positive *Pseudomonas aeruginosa*. In both groups of children, unadjusted values of weight, height and BMI *z-scores* increased after the implementation of the guidelines (Table 1). Figure 1 illustrates unadjusted means and 95% confidence intervals (CI) of the longitudinal weight, height and BMI *z-scores* over the period of 1998 to 2014. This means that in any

given year, some of the study participants had joined the registry later (e.g. newly diagnosed patients in 2007-2014), therefore resulting in the lower initial *z-scores* of these later entrants.

[Figure 1 about here please]

Figure 1A shows weight *z-scores* for children 2-5 years of age. Mean [95% CI] weight *z-scores* ranged from -0.03 [-0.17-0.11] in 1998 to -0.14 [-0.21-0.06] in 2006. Mean weight *z-scores* were 0.03 [-0.01-0.08] in 2014. In children 6-11 years of age (Figure 1B), mean weight *z-scores* ranged from -0.37 [-0.47-0.26] in 1998 to -0.18 [-0.30-0.05] in 2006 and to -0.07 [-0.30-0.15] in 2014. Similar trends can be observed in height *z-scores* and are depicted in Figures 1C and 1D. Mean [95% CI] BMI *z-scores* are shown in Figures 1E and 1F. In children 2-5 years of age the mean BMI scores were 0.11 [-0.03-0.24] in 1998 and 0.22 [0.17-0.28] in 2014 (Figure 1E). In children 6-11 years of age (Figure 1F), mean BMI *z-scores* were -0.06 [-0.16-0.03] in 1998 and -0.02 [-0.24-0.21] in 2014.

Table 2 summarises the results of the unadjusted GEE model analysis of mean changes in weight, height and BMI *z-scores* before and after implementation of the nutrition guidelines in 2006.

[Table 2 about here please]

For children 2-5 years of age, there was a decrease in weight (mean difference of -0.13, 95%CI [-0.15, -0.11]), height (mean difference of -0.17, 95%CI [-0.19, -0.15]) and BMI *z-scores* (mean difference of -0.13, 95%CI [-0.15-0.10]). In children 6-11 years of age, mean weight and height *z-scores* increased by 0.07, 95% CI [0.04-0.11] and 0.08, 95%CI [0.04-0.11] respectively. In this group of children, change in BMI *z-scores* was not statistically significant. However, when adjusted for sex, age, pancreatic status, dornase alfa, number of ever-colonised positive sample of *Pseudomonas aeruginosa* and G551D mutation, the model

demonstrated a significant increase in weight, height and BMI *z-scores* in both groups of children after the implementation of nutrition guidelines in 2006 (Table 3).

[Table 3 about here please]

*Survey results*

Nineteen (39%) responses were received from 48 doctors and dietitians invited to the survey. Thirteen (68%) of the survey respondents were dietitians and six (32%) were doctors working in CF for an average of 6.8 and 21.3 years respectively. Seven (37%) of the respondents worked in the field of CF both pre- and post- introduction of the nutritional guidelines, an additional three (16%) commenced during the introduction of the guidelines, and the remaining nine (47%) commenced after the 2006 guidelines were introduced. On average, the respondents spent 18.5 (9.9) hours per week in CF related work (Table 4A).

[Table 4 about here please]

Regarding acceptability and use, the guidelines were used by seventeen (89.5%) respondents. Fifteen (79%) respondents adopted the recommendations into their practice; 12 (63%) used the guidelines as part of their professional development and as a part of the orientation for the staff new to CF, 10 (53%) used them to advocate for change to practices and for education of clinicians and practitioners, and 8 (42%) used them to advocate for resources. The guidelines were understandable and well accepted by the team and patients/carers. Many reasons were cited as enablers to implementation, including that they were understandable and accepted by the team (47% of respondents cited each of these factors as specific enablers); and that they reflected current practices at the time of publication (68% citing this as an enabling factor) (Table 4A).

Regarding barriers to implementation, ten (53%) of the survey participants said there was inadequate staff resources, followed by insufficient resources and supporting educational

materials from four (21%) respondents, and limited high level evidence available for some guideline elements from five respondents (26%). Other structural barriers included lack of clinic space for consultations, inappropriate staff classification, high staff turnover and lack of mentoring support (Table 4A).

Respondents' experiences of applying the guidelines varied between dietitians and doctors. Dietitians viewed dietetic staffing levels as the most difficult recommendation to achieve, with the mean (SD) rating being 7.2 (3.5), where a rate of zero was considered as easy and 10 as hard. The next two most difficult recommendations were in relation to nutritional assessment for pregnancy and pancreatic enzyme replacement, with mean (SD) ratings of 4.0 (3.8) and 3.1 (4.1) respectively. Implementation of the other topics was considered easier (ratings between 1.9 and 2.8).

Doctors rated achieving dietetic staffing levels as the most difficult with the mean (SD) score of 7.5 (2.9), followed by nutritional assessment and management for pregnancy and lung transplantation with the mean (SD) score of 5 (3.1), and the nutrition-related co-morbid conditions (e.g. CF related diabetes, gastro-oesophageal reflux disease, distal intestinal obstruction syndrome, liver disease, bone health, pancreatitis) as easiest with the mean (SD) of 2 (2.8).

Survey participants were asked to rate the quality of the evidence on the following statements: 1) the guidelines are more suited to researchers than busy clinicians; 2) they are hard to explain to parents and patients; 3) they are too theoretical; 4) they are helpful because the categories are like a "traffic light guide", or 5) they are helpful in explaining to patients that science is not black and white (Table 4B). The average ratings on these topics were similar varied from 2.1 (statement 1) to 3.0 (statement 5) in dietitians, where a rate of zero was

considered as easy and 10 as hard. In doctors they varied from 2.0 (statements 1 and 2) to 4.0 (statement 4) in doctors.

**Discussion**

Optimal nutrition in patients with CF is very important and it is critical in children as it impacts growth [4, 39]. Moreover, nutritional status is positively associated with pulmonary function and survival [8]. King's et al [6] research of nutritional management of CF in Australia and New Zealand prior to the 2006 guidelines found that although consistent nutritional advice was provided by dietitians, there was great variation in the way in which energy requirements were calculated and in the criteria used to initiate and cease oral and enteral nutrition support. To facilitate optimal outcomes for patients with CF and to promote consistency and equity of healthcare and evidence based practice throughout Australia and New Zealand, the Australasian Clinical Practice Guidelines for nutrition in CF were released in 2006.

To compare nutrition outcomes before and after the implementation of the guidelines we chose two independent groups of children of 2-5 and 6-11 years of age. The older age group was much smaller than the younger group. When the registry was established in 1998, a contingent of children 6-11 years of age were added to the registry, but these children were in most cases diagnosed with CF earlier. Therefore, this contingent was larger than would be added in future years. In subsequent years, children would typically join the registry the year they were diagnosed or soon thereafter and, therefore, be assigned to the younger cohort.

The results of our study indicated that nutritional outcomes improved in children participating in the ACFDR after the implementation of the guidelines in 2006, suggesting that nutrition guidelines made a positive impact and were well accepted amongst clinicians. This finding became very much apparent after adjusting the GEE model for sex, age, pancreatic status,

dornase alfa (*Pulmozyme*), number of ever-colonised positive sample of *Pseudomonas aeruginosa* and G551D mutation. Our findings supports the results from the recent US studies which also demonstrated improvements in nutritional status in children with CF after implementation of quality improvement initiatives based on nutrition practice guidelines [40-42]. Notwithstanding, given the increasing prevalence of obese children in developed countries, it was important to rule out the possibility that improvement in nutritional outcomes of children with CF was partially due to changes in eating behaviour of a whole generation. A systematic review of 264,905 Australians aged 2–18 years conducted by Olds et al [43] demonstrated a plateau, or only slight increase, in the percentage of boys and girls classified as overweight or obese, with almost no change in 2000-2010. This suggests that the prevalence of overweight and obesity seemed to have flattened over the study period and had not followed the anticipated exponential trajectory of increase in weight and BMI in a healthy paediatric population.

Nearly 40% of invited survey participants expressed their views on the nutritional guidelines. Overall, they agreed they were useful in change of practice. The majority of respondents worked equally with inpatients and outpatients (69%), which indicates that results of the survey can be generalised across both the inpatient and outpatient environments.

Lack of adequate staff resources was most frequently identified as a factor, which made the 2006 nutrition guidelines difficult to implement. This could potentially indicate that the issue of shortfalls in recommended staffing levels [6, 8], observed to be at 0.15 full-time equivalent per 50 patients compared to recommended 0.5 full-time equivalent per 50 to 75 patients in the CF Australia Standards of Care 2008 [32], have still not fully been addressed.

Increasing difficulty in application of the guidelines as children age may reflect issues such as the difficulty in monitoring eating and medication use at school, and the development of

independence, which may impact adherence. The slightly increasing difficulty in application of the guidelines in school-aged children and adolescents compared with infants and the newly diagnosed patient, may reflect increasing complexity of care needs including differing developmental and environmental barriers to implementation that occur during these age groups. Infant care includes supporting breast feeding, monitoring calorific intake and introducing Pancreatic Enzyme Replacement Therapy (PERT) at meal times. As children grow, common behaviours of food refusal and fussy eating make implementing dietary intake guidelines difficult and starting school requires training children to take tablets and the education of school staff. As adolescents become more independent, rejection of CF treatments may occur at time when adequate energy is required for growth. These barriers are acknowledged and explored in the guidelines. Recommendations of nutrition in pregnancy may have been viewed as difficult to implement due the relative rarity of pregnancy in CF paediatric care in Australia.

The respondents judged the categories of evidence for the guidelines for the most part positively, as the survey results indicated they were just as suited to clinicians as to researchers; and they were easy to explain to parents and patients, and were not too theoretical. More neutral survey responses were observed regarding the utility of the guidelines as a traffic light system, and the helpfulness of the categories to explain how some research is better than others [6, 44].

*Strengths and limitations*

Registry data is a high quality source of nutritional outcome information for CF patients, and is an ideal tool for conducting such analyses and evaluating effectiveness of the nutritional strategies and the efforts to obtain optimal growth in CF children, and the importance to maintain adequate nutritional status in patients with CF [41].

Our study had a large sample size and number of participants with comprehensive data of nutritional outcomes across various groups of patients with CF. All eligible patients on the ACFDR were identified through the health records at participating ACFDR sites, thus reducing the risk of selection bias. The registry also provides over 90% of the population with CF in Australia and has collected diagnostic and outcome data since 1998 with the completeness of clinical measurements including pulmonary function and BMI being close to 100%.

However, the study does have some limitations. The registry was established in 1998 and over the years it has been updated to include new data elements, however not all of the new data elements, particularly those related to the confounders, have been completely collected. For example, in 2015 microbiology data was reported for only 65% of the registry participants [2]. In addition, the registry does not collect data on chronic infection for those with *Pseudomonas aeruginosa*, and the age of acquisition of chronic infection might play an important role in determining effects on nutritional status. Furthermore, it is possible that there were improvements in symptomatic pulmonary therapy as well as more caretaking in specialised CF centres during the period from 1998-2014 that could also influence the nutritional status. However, the information on the above-mentioned factors has not been collected systematically and, therefore, it could not be considered as a confounding factor in the analysis. Finally, the ACFDR uses routinely collected data, with records entered by hospital staff, and so we cannot exclude the possibility of data coding and input errors.

The moderate response rate may reflect factors such as staffing changes. It is also possible that some of those who did not respond might have been relatively new to the area, and, therefore felt less equipped to answer questions about the introduction of the guidelines some year earlier.

The results of the survey provide a useful summary of the achievements and limitations of the guidelines; however, a small sample of respondents may reflect selection bias and not be broadly representative.

*Future directions*

Findings from this study suggest that in children participating in the ACFDR, nutritional status improved after the implementation of the 2006 nutrition guidelines. The revised Australasian nutrition guidelines for CF were released in late 2017 [45]; therefore, there is an opportunity to use the findings from this research to identify enablers and barriers to guideline implementation and inform implementation strategies for the updated guidelines and for other clinical practice guidelines for CF. Ongoing analysis of nutritional outcomes using periodic data from the ACFDR, and continual identification of emerging potential confounders to consider in such analyses, will be essential to evaluate the success of these and other significant nutritional initiatives that aim to improve the care and outcomes for individuals with CF and their families into the future.

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**Conflicts of interests**

The authors declare that they have no conflicts of interests.

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**Tables**

Table 1. Demographic characteristics of the study participants at the year they joined the ACFDR (N = 2,304) diagnosed with CF in 1998-2014.

| **Characteristics** | **2 - 5 years of age** | **6 - 11 years of age** |
|---|---|---|
| Patients, N (%) | 1,655 (71.8) | 649 (28.7) |
| Sex | | |
| *Male, N (%)* | 836 (50.5) | 331 (51.0) |
| *Female, N (%)* | 819 (49.5) | 318 (49.0) |
| G551D mutation, N (%) | 120 (7.3) | 39 (6.1) |
| Records with clinical measurements 1998-2014, N (%) | 13,437 (73.6) | 4,824 (26.4) |
| Records with clinical measurements prior to the intervention*, N (%) | 4,146 (30.8) | 3,595 (74.5) |
| Records indicating Dornase alfa use 1998-2014, N (%) | 3,382 (25.3) | 1,745 (36.5) |
| Records indicating pancreatic insufficiency, 1998-2014, N (%) | 11,315 (85.2) | 3,698 (78.1) |
| Records with positively populated *Pseudomonas aeruginosa* 1998-2014, N (%) | | |
| *One* | 2,061 (35.9) | 1,079 (31.7) |
| *Two* | 795 (13.9) | 682 (20.0) |
| *Three* | 45 (0.8) | 107 (3.1) |
| *Four* | 93 (1.6) | 6 (0.2) |
| Weight *z-score prior to the* intervention*, mean [95% CI] | -0.09 [-0.13; -0.07] | -0.35 [-0.38; -0.31] |
| Weight *z-score post-intervention**, mean [95% CI] | 0.01 [-0.01; 0.03] | -0.11 [-0.17; -0.06] |
| Height *z-score prior to the intervention**, mean [95% CI] | -0.22 [-0.25; -0.19] | -0.46 [-0.49; -0.43] |
| Height *z-score post-intervention**, mean [95% CI] | -0.23 [-0.25; -0.21] | -0.23 [-0.30; -0.18] |
| BMI *z-score prior to the intervention**, mean [95% CI] | 0.12 [0.09; 0.15] | -0.11 [-0.14; -0.08] |
| BMI *z-score post- intervention**, mean [95% CI] | 0.24 [0.22; 0.25] | 0.02 [-0.03; 0.07] |
| *Note: *implementation of the nutrition guidelines in 2006* | | |

Table 2. Mean changes in weight, height and body mass index (BMI) *z-scores* before and after the implementation of the 2006 nutrition guidelines (unadjusted analysis)

| **Outcome** | **2-5 years of age** | | | | **6-11 years of age** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Mean difference*** | **95% CI** | | **p-value** | **Mean difference*** | **95% CI** | | **p-value** |
| Weight z-score | -0.13 | -0.15 | -0.11 | <0.001 | 0.07 | 0.04 | 0.11 | <0.001 |
| | | | | | | | | |
| Height z-score | -0.17 | -0.19 | -0.15 | <0.001 | 0.08 | 0.04 | 0.11 | <0.001 |
| | | | | | | | | |
| BMI z-score | -0.13 | -0.15 | -0.11 | <0.001 | -0.02 | -0.06 | 0.02 | 0.423 |
| *Note: * reference group is pre-intervention (i.e. before the implementation of the nutrition guidelines in 2006). All p-values from generalised estimating equation models correctly accounting for within patient correlation using the exchangeable correlation matrix.* | | | | | | | | |

Table 3. Mean changes in weight, height and body mass index (BMI) z-scores before and after the implementation of the 2006 nutrition guidelines (adjusted analysis)

| **Outcome** | **2-5 years of age** | | | | **6-11 years of age** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Mean difference*** | **95% CI** | | **p-value** | **Mean difference*** | **95% CI** | | **p-value** |
| Weight z-score | 0.14 | 0.08 | 0.20 | <0.001 | 0.11 | 0.04 | 0.18 | 0.001 |
| | | | | | | | | |
| Height z-score | 0.04 | -0.01 | 0.09 | 0.109 | 0.11 | 0.05 | 0.17 | <0.001 |
| | | | | | | | | |
| BMI z-score | 0.18 | 0.12 | 0.24 | <0.001 | 0.08 | 0.01 | 0.17 | 0.029 |
| *Note: * reference group is pre-intervention (i.e. before the implementation of the nutrition guidelines in 2006). All p-values from generalised estimating equation models correctly accounting for within patient correlation using the exchangeable correlation matrix. Estimates adjusted for sex, age, pancreatic status, use of dornase alfa (Pulmozyme), number of positive Pseudomonas aeruginosa and G551D mutation. Age represents age at the first presentation to the registry.* | | | | | | | | |

Table 4. Summary of the dietitians and doctors survey responses. Table 4A summarises responses to categorical survey questions, shown as n (%). Table 4B provides responses to survey rating questions, presented as mean (SD).

Table 4A

| **Survey questions** | **Dietitians (n = 13)** | **Doctors (n = 6)** | **Overall (n = 19)** |
|---|---|---|---|
| Mean (SD) time in working in CF, years | 6.8 (4.8) | 21.3 (11.3) | 11.4 (9.9) |
| **Type of patients seen, n (%)** | | | |
| *Inpatients* | 1 (7.7) | 0 (0) | 1 (5.3) |
| *Outpatients* | 3 (23.1) | 2 (33.3) | 5 (26.3) |
| *Both* | 9 (69.2) | 4 (66.7) | 13 (68.4) |
| Mean (SD) time spent on CF work per week, hours | 19.9 (8.2) | 15.3 (13.2) | 18.5 (9.9) |
| Used the guidelines, n (%) | 13 (100) | 4 (66.7) | 17 (89.5) |
| **Ways of how the guidelines were used, n (%)*** | | | |
| *Adopted into practice for assessments* | 12 (93.3) | 3 (50) | 15 (78.9) |
| *As part of orientation for those new to CF* | 9 (69.2) | 3 (50) | 12 (63.2) |
| *As professional self-development* | 9 (69.2) | 3 (50) | 12 (63.2) |
| *For education of clinicians/practitioners* | 8 (61.5) | 2 (33.3) | 10 (52.6) |
| *To advocate for resources* | 7 (53.8) | 1 (16.7) | 8 (42.1) |
| *To advocate for change to practices* | 9 (69.2) | 1 (16.7) | 10 (52.6) |
| **Enablers that helped to implement the guidelines, n (%)*** | | | |
| *Reflected current practice* | 10 (76.9) | 3 (50) | 13 (68.4) |
| *A simple change was required* | 3 (23.1) | 3 (50) | 6 (31.6) |
| *Not costly* | 3 (23.1) | 2 (33.3) | 5 (26.3) |
| *Well accepted (by team/patients/carers)* | 7 (53.8) | 2 (33.3) | 9 (47.4) |
| *Understandable* | 7 (53.8) | 2 (33.3) | 9 (47.4) |
| **Factors that made the guidelines hard to implement, n (%)*** | | | |
| *No or limited high level evidence available for some topics* | 4 (30.8) | 1 (16.7) | 5 (26.3) |
| *Lack of adequate staff resources* | 8 (61.5) | 2 (33.3) | 10 (52.6) |
| *Insufficient funding for products* | 3 (23.1) | 1 (16.7) | 4 (21.1) |
| *Lack of educational material* | 3 (23.1) | 1 (16.7) | 4 (21.1) |
| *Not accepted by CF team members* | 1 (7.7) | 0 | 1 (5.3) |
| **Other structural barriers for implementation, n (%)*** | | | |
| *High staff turnover* | 1 (7.7) | 1 (16.7) | 2 (10.5) |
| *Inappropriate staff grading/classification* | 3 (23.1) | 0 (0) | 3 (15.8) |
| *Lack of clinic space for consultations* | 5 (38.5) | 1 (16.7) | 6 (31.6) |
| *Lack of mentoring support* | 2 (15.4) | 0 (0) | 2 (10.5) |

**Multiple responses allowed per question, therefore numbers add to more than 100%*

Table 4B

| **Survey questions** | **Dietitians (n = 13)** | **Doctors (n = 6)** | **Overall (n = 19)** |
|---|---|---|---|
| **Guideline recommendation topics, mean (SD)[#]** | | | |
| *Dietetic staffing levels* | 7.2 (3.5) | 7.5 (2.9) | 7.3 (3.3) |
| *Nutritional assessment* | 1.9 (1.2) | 5 (3.6) | 2.7 (2.4) |
| *Nutritional requirements for macronutrients, vitamins and mineral* | 2.7 (1.4) | 4.3 (2.9) | 3.1 (1.9) |
| *Pancreatic enzyme replacements* | 2.3 (1.4) | 4.3 (3.6) | 2.8 (2.2) |
| *Nutritional assessment for pregnancy* | 4 (3.8) | 5 (-) | 4.1 (3.6) |
| *Nutritional management for lung transplantation* | 2.6 (3.8) | 5 (3.1) | 3.1 (3.3) |
| *Blood testing* | 2.8 (1.4) | 2.5 (4.4) | 2.7 (2.3) |
| *Other tests (e.g. gastroenterological test, pancreatic function tests)* | 2.8 (1.7) | 5.3 (3.8) | 3.4 (2.5) |
| *Routine nutritional interventions* | 2.5 (2.1) | 4 (3.9) | 2.9 (2.6) |
| *Nutrition-related co-morbid conditions (e.g. CF related diabetes, GOR, DIOS, liver disease, bone health, pancreatitis)* | 2.8 (0.9) | 2 (2.8) | 2.6 (1.6) |
| *Infants and newly diagnosed patients* | 1.9 (1.2) | 3.5 (3.7) | 2.3 (2.1) |
| *Young children* | 2.4 (1.4) | 4 (3.2) | 2.8 (2.0) |
| *Adolescents* | 2.7 (1.8) | 4.3 (2.9) | 3.1 (2.2) |
| **Guideline evidence categories, mean (SD) [#]** | | | |
| *More suited to researchers than busy clinicians* | 2.1 (1.5) | 2 (1.8) | 2.0 (1.5) |
| *Hard to explain to parents/patients* | 2.3 (1.8) | 2 (1.8) | 2.2 (1.6) |
| *Too theoretical* | 2.4 (1.3) | 2.5 (0.6) | 2.4 (1.1) |
| *Helpful because of a 'traffic like guide'* | 2.8 (1.1) | 4 (0.8) | 3.1 (1.1) |
| *Helpful in explaining to patients that science is not black and white* | 3.0 (1.3) | 3.8 (0.9) | 3.2 (1.3) |

*#Participants were asked to rate topic areas on a scale from 0 (easy) to 10 (hard)*

## Figures

**Figure 1.** Unadjusted weight, height and BMI *z-scores* before and after the release of the 2006 nutrition guidelines (shown as a dashed line). Figure A and B show mean and 95% confidence intervals (CI) weight *z-scores* for children of 2-5 and 6-11 years of age respectively. Figure C and D show mean and 95% CI height *z-scores* for children of 2-5 and 6-11 years of age. Figure E and F show mean and 95% CI BMI *z-scores* for children of 2-5 and 6-11 years of age. The mean values and the 95% confidence intervals are unadjusted.