children

MDPI

Article

Standards of Nutritional Care for Patients with Cystic Fibrosis: A Methodological Primer and AGREE II Analysis of Guidelines

Maria G. Grammatikopoulou [1,2,3,4], Tonia Vassilakou [5], Dimitrios G. Goulis [3], Xenophon Theodoridis [6], Meletios P. Nigdelis [3], Arianna Petalidou [2], Konstantinos Gkiouras [2,6], Dimitrios Poulimeneas [7], Olga Alexatou [7], Kyriaki Tsiroukidou [4], Georgios Marakis [8], Zoe Daniil [9] and Dimitrios P. Bogdanos [2,*]

1 Department of Nutritional Sciences & Dietetics, Faculty of Health Sciences, Alexander Campus, International Hellenic University, 57400 Thessaloniki, Greece; maria@ihu.gr
2 Department of Rheumatology and Clinical Immunology, Faculty of Medicine, School of Health Sciences, University of Thessaly, 41110 Larissa, Greece; arianna.petalidou@gmail.com (A.P.); kostasgkiouras@hotmail.com (K.G.)
3 Unit of Reproductive Endocrinology, 1st Department of Obstetrics and Gynecology, Papageorgiou General Hospital, Medical School, Aristotle University of Thessaloniki, 56429 Thessaloniki, Greece; dgg@auth.gr (D.G.G.); meletis.nigdelis@gmail.com (M.P.N.)
4 3rd Department of Pediatrics, Hippokration General Hospital of Thessaloniki, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece; ktsiroukidou@gmail.com
5 Department of Public Health Policy, School of Public Health, University of West Attica, Athens University Campus, 11521 Athens, Greece; tvasilakou@uniwa.gr
6 Medical School, Faculty of Health Sciences, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece; xenofontheodoridis@gmail.com
7 Department of Nutrition & Dietetics, Harokopio University, 17676 Athens, Greece; dpoul@hua.gr (D.P.); olga_alexatou@hotmail.com (O.A.)
8 Nutrition and Food Standards Unit, Risk Assessment and Nutrition Directorate, Hellenic Food Authority, 11526 Athens, Greece; gmarakis@efet.gr
9 Department of Respiratory Medicine, Faculty of Medicine, School of Health Sciences, University of Thessaly, 41110 Larissa, Greece; zdaniil@med.uth.gr
* Correspondence: bogdanos@med.uth.gr

Abstract: Although many Clinical Practice Guidelines (CPGs) have been published for the care of patients with Cystic Fibrosis (CF), including a variety of nutrition recommendations, the quality of these CPGs has never been evaluated. The aim of this study was to compare, review, and critically appraise CPGs for the nutritional management of CF, throughout the lifespan. We searched PubMed, Guidelines International Network (GIN), ECRI Institute, and Guidelines Central for CPGs, with information on the nutritional management of CF. Retrieved CPGs were appraised by three independent reviewers, using the Appraisal of Guidelines, Research and Evaluation II (AGREE II) instrument and checklist. A total of 22 CPGs (seven solely nutrition oriented), by 14 different publishers, were retrieved. The Thoracic Society of Australia and New Zealand CPGs scored the highest overall quality (94.4%), while the Paediatric Gastroenterology Society/Dietitians Association of Australia CPGs had the lowest score (27.8%). Great variation in AGREE II domain-specific scores was observed in all CPGs, suggesting the existence of different strengths and weaknesses. Despite the availability of several CPGs, many appear outdated, lacking rigor, transparency, applicability, and efficiency, while incorporating bias. Considering that CPGs adherence is associated with better outcomes and the need for improving life expectancy in patients with CF, the development of CPGs of better quality is deemed necessary.

Keywords: nutrition intervention; medical nutrition therapy; pulmonary function; critical appraisal; nutrition recommendation; evidence-based dietetics; clinical practice; clinical practice guidelines; pulmonology

Citation: Grammatikopoulou, M.G.; Vassilakou, T.; Goulis, D.G.; Theodoridis, X.; Nigdelis, M.P.; Petalidou, A.; Gkiouras, K.; Poulimeneas, D.; Alexatou, O.; Tsiroukidou, K.; et al. Standards of Nutritional Care for Patients with Cystic Fibrosis: A Methodological Primer and AGREE II Analysis of Guidelines. *Children* **2021**, *8*, 1180. https://doi.org/10.3390/children8121180

Academic Editor: Sari A. Acra

Received: 31 October 2021
Accepted: 9 December 2021
Published: 14 December 2021

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disease that is caused by mutations in the gene for the CF trans-membrane conductance regulator (CFTR), which encodes an ion channel protein, with more than 2000 mutations identified to date [1–3]. CF affects appetite, nutritional status, and pulmonary function in a progressive manner, with all synergistically resulting in poor health outcomes [4]. Malabsorption, gastrointestinal dysfunction, genetic modifiers, and chronic and progressive pulmonary infection compromise nutritional status, resulting in growth failure [5–7]. As far as nutritional status and pulmonary function are concerned, a two-way relationship exists, with each one affecting the other [8]. As a result, optimizing nutrition is pivotal, with medical nutrition therapy (MNT) being front and foremost in CF management. Recent advances in medicine and supplements [9], multidisciplinary care, the use of more holistic treatment approaches, and adherence to specific dietary protocols have all levelled up the delivery of nutrition intervention among CF patients, reducing growth failure [10,11].

CF-MNT adherence has been associated with ameliorated nutritional status, improved lung function, and better prognosis [12,13]; however, according to the literature, sub-optimal treatment adherence is observed in the majority of patients [14]. On the flipside, CF-specific training opportunities for physicians are limited, especially for adult patients [15], and, as far as clinical practice guidelines (CPGs) are concerned, they exhibit several controversies [16], limiting their adherence and delivery from the physician point of view.

Clear, precise, unbiased, and evidence-based CPGs are needed to promote physician adherence and improve patient prognosis. As such, during the last decade, the quest to compare and appraise CPGs has become a focus. Given that CF-specific CPGs have never been evaluated, the present study aimed to compared, review, and critically appraise CPGs for the nutritional management of CF, throughout the lifespan.

The aim of the present study was (1) to systematically review all CPGs on the nutritional recommendations and CF-MNT for patients with CF, and (2) to critically appraise them. The research question was: What is the quality of CPGs regarding MNT in CF?

2. Materials and Methods

2.1. PICAR, Search Strategy, Inclusion, and Exclusion Criteria

The PICAR framework, a modification of the PICO(T/S) [17], developed by the University of Ottawa Heart Institute, was applied to shape the research question and define the CPG eligibility criteria [18]. The PICAR strategy applied in the present review is detailed in Table 1.

Table 1. Description of the PICAR strategy.

PICAR Acronym Criteria	PICAR Items Relevant to Screening CPGs for Inclusion
(P) Population	Patients with Cystic fibrosis, throughout the lifespan.
(I) Intervention	Any dietary intervention or MNT for patients with cystic fibrosis (i.e., micronutrient supplementation, provision of energy or macronutrient intake, management of lung transplantation, management of CFRD, etc.).
(C) Comparators, Comparison, and 'key' content	Any comparator or comparison. No 'key' CPG content is of interest.
(A) Attributes of the CPGs	Eligible CPGs were: (1) CPGs, Practice, or Consensus Papers, (2) published in the English language, (3) in full-text format, (4) until August 2018, (5) from professional or governmental organizations, with (6) nutrition-related recommendations, (7) intended for health professionals, (8) without any limitation in their quality based on the AGREE II.
(R) Recommendation characteristics and other considerations	Not applicable.

AGREE: Appraisal of Guidelines, Research and Evaluation [19]; CFRD: Cystic Fibrosis-Related Diabetes; CPG: Clinical Practice Guideline; MNT: Medical Nutrition Therapy; PICAR: Population, Intervention, Comparator, Attributes, Recommendations [18].

A systematic search was conducted in PubMed, Guidelines International Network (GIN), ECRI Institute, Guidelines Central, and gray literature, until 2019, aiming to retrieve CPGs and Consensus Statements with information on the nutritional management of CF.

The keywords used for the search process included (cystic fibrosis), (nutrition), (clinical practice guidelines), (consensus statements), (nutritional management), (nutritional therapy), (diet therapy), and (pulmonary care).

2.2. Inclusion and Exclusion Criteria

Inclusion criteria involved CPGs (1) published in the English language, (2) available in full-text electronic format, (3) for the care of patients with CF, (4) including nutrition recommendations, and (5) intended for healthcare professionals. Exclusion criteria involved CPGs (1) published in languages other than English, (2) for the diagnosis of CF, (3) intended for CF patients, caretakers or family members, (4) lacking nutrition recommendations.

2.3. Appraisal of CPGs

Retrieved CPGs were appraised by three independent reviewers using the Appraisal of Guidelines, Research and Evaluation II (AGREE II) instrument [19] and the AGREE II checklist [20]. The AGREE II is a validated tool assessing the transparency and methodological rigor of published CPGs, used in medical and nutrition practice guidelines [21]. Scores were applied in each AGREE domain concerning the scope and purpose of the retrieved CPGs, completeness of stakeholder involvement, scientific rigor, presentation clarity, applicability of the recommendations, and editorial independence. When differences were observed in individual reviewer scores, a fourth reviewer solved the issue after conversation with the review panel. Overall quality scores were calculated for each individual domain and CPG while, additionally, each reviewer advocated for or against the use of specific CPGs for the nutritional management of CF.

2.4. CPGs Review and MNT Information

Individual nutrition recommendations were reviewed, categorized, and entered in an excel file by each reviewer independently, to produce an overview of the CF-MNT recommendations.

3. Results

3.1. Retrieved CPGs and Their Characteristics

A total of 22 CPGs fulfilled the predefined criteria. They were published by the Thoracic Society of Australia and New Zealand (TSANZ) [22]; by a joint committee of the European Society for Clinical Nutrition and Metabolism (ESPEN), the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), and the European Cystic Fibrosis Society (ECFS) [23]; the ECFS alone [24–29]; the Cystic Fibrosis Foundation (CFF) [30–36]; a united effort by the American Diabetes Association (ADA), the CFF and the Pediatric Endocrine Society (PES) [37], a joint committee by the CFF and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHN) [38]; the Cystic Fibrosis Trust (CFT) [39]; the UK National Institute for Health and Care Excellence (NICE) [40]; the International Society for Pediatric and Adolescent Diabetes (ISPAD) [41]; a joint committee by the Pediatric Gastroenterology Society (PGS) and the Dietitians Association of Australia (DAA) [42]; and the Sociedade Brasileira de Pneumologia e Tisiologia (SBPT) [43]. Table 2 details the main characteristics of the eligible CPGs.

The majority of CPGs were issued by professional organizations and only one was developed by a government authority [40]. They included recommendations for patients of all age groups, including infants, children, and adolescents, as well as adults. Total page numbers ranged from 4 [34] to 768 [40]. Guidelines were published between the year 1995 [34] to 2018 [25].

Table 2. General description of the included guidelines and their scope.

Advising Body	Year	Origin	Aim			Age Group			Organization		Total Pages
			CF Care with Nutritional Advice	CF MNT	Management of CF Issues, Including Nutritional Care	Infants	Children/Adolescents	Adults	Professional	State	
ADA/CFF/PES [37]	2010	US			CFRD		√	√	√		12
CFF [34]	1995	US	√		PERT	√	√	√	√		4
CFF [30]	2008	US		√			√	√	√		8
CFF [32]	2009	US	√			√			√		21
CFF [36]	2009	US			CFTR-Related MS	√	√	√	√		22
CFF [33]	2012	US			Vitamin D deficiency	√	√	√	√		12
CFF [31]	2016	US	√			√	√				28
CFF [35]	2016	US		√	EN feeding		√	√	√		12
CFF/NASPGHAN [38]	2002	US		√			√		√		14
CFT [39]	2016	UK		√		√	√	√	√		60
ECFS [24]	2002	EU		√		√	√	√	√		25
ECFS [29]	2008	EU	√		Pregnancy			√	√		31
ECFS [28]	2010	EU	√			√			√		7
ECFS [27]	2011	EU			DIOS		√	√	√		5
ECFS [26]	2014	EU	√		LTX		√	√	√		22
ECFS [25]	2018	EU	√			√	√	√	√		26
ESPEN/ESPGHAN/ECFS [23]	2016	EU		√		√	√	√	√		21
ISPAD [41]	2018	International	√		CFRD		√		√		11
NICE [40]	2017	UK	√			√	√	√		√	768
PGS/DAA [42]	1999	AU		√		√	√	√	√		5
SBPT [43]	2017	BR	√			√	√	√	√		27
TSANZ [22]	2017	AU & NZ		√		√	√	√	√		284

ADA, American Diabetes Association; CF, Cystic Fibrosis; CFF, Cystic Fibrosis Foundation; CFRD, Cystic Fibrosis-Related Diabetes; CFT, Cystic Fibrosis Trust; CFTR-Related MS, Cystic Fibrosis transmembrane conductance regulator-related Metabolic Syndrome; DAA, Dietitians Association of Australia; DIOS, distal intestinal obstruction syndrome; EN, Enteral nutrition; ESPEN European Society for Clinical Nutrition and Metabolism; ESPGHAN, European Society for Pediatric Gastroenterology, Hepatology and Nutrition; ECFS, European Cystic Fibrosis Society; ISPAD, International Society for Pediatric and Adolescent Diabetes; LTX, lung transplantation; MNT, Medical Nutrition Therapy; NASPGHAN, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; NICE, National Institute for Health and Care Excellence; PERT, Pancreatic Enzyme Replacement Therapy; PES, Pediatric Endocrine Society; PGS, Paediatric Gastroenterology Society; SBPT, Sociedade Brasileira de Pneumologia e Tisiologia; TSANZ, Thoracic Society of Australia and New Zealand.

3.2. AGREE Scoring of Included Guidelines

Of the 22 CPGs retrieved in total, the TSANZ [22] guidelines obtained the highest score in four out of six main domains of the AGREE II instrument. Subsequently, the TSANZ [22] CPG was suggested by all reviewers for adherence in clinical practice without needing modifications and achieved the highest score in the overall CPGs' quality assessment. On the other hand, the ECFS [24] CPGs yielded low scores in all domains and the overall assessment, while it was not recommended by one of the experts. Detailed scores received for each domain and subdomain, as well as expert recommendations, are presented in Figure 1.

3.3. Nutrition Recommendations in the Included Guidelines

Figures 2 and 3 present a summary of nutrition recommendations for the management of CF and CF-related complications. Among the 14 advising bodies, the TSANZ [22], CFT [39], and the joint guidelines published by the ESPEN/ESPGHAN/ECFS [23] incorporated the majority of MNT recommendations. On the other hand, the joint committee by PSG/DAA [42] included the least amount of nutrition recommendations.

3.3.1. General Features of the Delivery MNT in Patients with CF

With respect to the involvement of dietitians in the delivery of MNT in patients with CF, several but not all CPGs advocate for the involvement of dietitians. Nutritional screening is an important component mentioned by the majority of CPGs, with the need for routine screening highlighted by some. The need for nutrition education of patients was mentioned by six CPGs only, whereas assessment of patient nutritional status, with sex- and age-specific cutoffs, was provided as a recommendation by the ECFS [25,28].

3.3.2. Energy and Nutrient Intake

As for the adequate provision of energy, most CPGs recommended 110–200% of the respective energy intake of the general population, although different ranges were also suggested (120–150% of the general population goal), mainly for patients with CFRD [25,28,37,41].

With respect to the protein intake, great diversity was presented, with the ISPAD [41] suggesting a consumption equal to 200% of the recommended nutrient intake (RNI), the TSANZ [22] proposing an intake ranging between 15% and 20% of the energy intake (EI), and the CFF [31] suggesting different intakes per distinct age tiers of minor patients.

On the other hand, ideal fat intake appears to be universally more liberal, ranging between 35% and 40% of the EI, irrespective of CFRD diagnosis [37,38,41,43].

As for carbohydrate, recommendations were only provided for patients with CFRD, suggesting an individualized (45–50% of the EI) but monitored consumption, aiming to achieve glycemic control, while avoiding non-nutritive substances and sugary beverages [37,41].

Recommendations for fiber advocated for the encouragement of intake among the well-nourished patients, although, among the poorly nourished, it may reduce energy intake [41]. On the other hand, the TSANZ [22] suggested the intake of 14–30 g on a daily basis. Finally, with respect to patients scheduled for LTX, care should be provided for the adequate intake of fluid and fiber post-surgery, in order to activate bowel movements within 48–72 h [26].

AGREE domains:	ADA/ CFF/PES [37]	CFF [34]	CFF [30]	CFF [32]	CFF [36]	CFF [33]	CFF [31]	CFF [35]	CFF/ NASPGHAN [38]	CFT [39]	ECFS [24]	ECFS [29]	ECFS [28]	ECFS [27]	ECFS [26]	ECFS [25]	ESPEN/ ESPGHAN/ ECFS [23]	ISPAD [41]	NICE [40]	PGS/DAA [42]	SBPT [43]	TSANZ [22]
1. Scope & purpose:	92.6	88.3	96.3	98.1	92.6	90.7	98.1	83.3	88.9	94.4	81.5	92.6	94.4	85.2	96.3	88.9	92.6	66.7	85.2	77.8	98.1	**100**
1a. Objectives	88.9	77.8	88.9	100	94.4	88.9	94.4	83.3	77.8	94.4	66.7	94.4	100	83.3	100	83.3	77.8	61.1	77.8	66.7	100	100
1b. Questions	94.4	83.3	100	100	88.9	88.9	100	83.3	88.9	88.9	83.3	88.9	88.9	77.8	94.4	94.4	100	55.6	88.9	77.8	100	100
1c. Population	94.4	88.9	100	94.4	94.4	94.4	100	83.3	100	100	94.4	94.4	94.4	94.4	94.4	88.9	100	83.3	88.9	88.9	94.4	100
2. Stakeholder involvement:	**51.9**	92.6	**100**	64.8	40.7	22.2	63.0	63.0	94.4	83.3	29.6	50.0	40.7	48.1	40.7	61.1	38.9	33.3	87.0	31.5	42.6	96.3
2a. Group membership	88.9	94.4	100	100	88.9	66.7	88.9	88.9	88.9	100	77.8	88.9	88.9	88.9	88.9	88.9	88.9	100	83.3	94.4	83.3	100
2b. Target populations preferences/views	11.1	94.4	100	0	11.1	0	22.2	11.1	100	50.0	11.1	11.1	11.1	11.1	11.1	11.1	27.8	0	77.8	0	11.1	94.4
2c. Target users	55.6	88.9	100	94.4	22.2	0	77.8	88.9	94.4	100	0	50.0	22.2	44.4	22.2	83.3	0	0	100	0	33.3	94.4
3. Rigor:	63.2	22.2	70.8	77.8	56.9	70.1	81.3	40.3	27.1	34.7	24.3	51.4	63.2	44.4	53.5	21.5	81.3	8.3	67.4	15.3	66.7	**90.0**
3a. Search methods	72.2	0	100	100	61.1	100	94.4	44.4	0	33.3	0	66.7	77.8	61.1	61.1	0	100	0	83.3	5.6	94.4	88.9
3b. Evidence criteria	72.2	0	100	100	55.6	100	94.4	66.7	22.2	0	11.1	61.1	83.3	55.6	55.6	0	88.9	0	83.3	5.6	88.9	94.4
3c. Evidence pros & cons	72.2	0	83.3	66.7	66.7	94.4	88.9	44.4	5.6	27.8	16.7	44.4	72.2	44.4	66.7	16.7	83.3	33.3	83.3	0	66.7	72.2
3d. Recommendation formulation	83.3	44.4	94.4	83.3	77.8	88.9	100	33.3	83.3	22.2	27.8	55.6	83.3	55.6	66.7	50.0	100	0	83.3	5.6	83.3	100
3e. Benefits & harms consideration	50.0	55.6	22.2	72.2	55.6	61.1	77.8	61.1	11.1	77.8	61.1	61.1	50.0	44.4	55.6	11.1	88.9	0	72.2	55.6	61.1	94.4
3f. Recommendations & evidence link	88.9	55.6	94.4	83.3	83.3	72.2	100	72.2	72.2	72.2	77.8	77.8	88.9	61.1	72.2	94.4	94.4	33.3	88.9	50.0	94.4	100
3g. External review	33.3	22.2	61.1	16.7	55.6	44.4	83.3	0	22.2	44.4	0	44.4	50.0	33.3	50.0	0	94.4	0	16.7	0	44.4	66.7
3h. Updating procedures	33.3	0	11.1	100	0	0	11.1	0	0	0	0	0	0	0	0	0	0	0	27.8	0	0	100
4. Presentation clarity:	79.6	46.3	63.0	92.6	70.4	85.2	**94.4**	79.6	75.9	92.6	90.7	87.0	66.7	57.4	77.8	59.3	90.7	66.7	72.2	75.9	81.5	88.9
4a. Specific, clear recommendations	100	72.2	83.3	94.4	83.3	94.4	100	94.4	94.4	94.4	94.4	100	88.9	66.7	94.4	77.8	94.4	100	83.3	94.4	100	94.4
4b. Management options	44.4	11.1	16.7	88.9	38.9	72.2	83.3	50.0	38.9	83.3	77.8	61.1	27.8	38.9	38.9	5.6	83.3	0	66.7	44.4	44.4	72.2
4c. Identifiable key recommendations	94.4	55.6	88.9	94.4	88.9	88.9	100	94.4	94.4	100	100	100	83.3	66.7	100	94.4	94.4	100	66.7	88.9	100	100
5. Applicability:	34.7	13.9	16.7	43.1	34.7	44.4	41.7	23.6	26.4	44.4	15.3	37.5	31.9	26.4	31.9	51.4	47.2	22.2	76.4	26.4	30.6	**80.6**
5a. Application facilitators & barriers	38.9	27.8	0	44.4	38.9	44.4	55.6	38.9	38.9	61.1	5.6	44.4	44.4	33.3	27.8	66.7	22.2	27.8	66.7	38.9	33.3	77.8
5b. Implementation of advice/tools	33.3	5.6	0	44.4	27.8	11.1	0	0	0	5.6	0	38.9	33.3	22.2	38.9	44.4	11.1	0	94.4	27.8	33.3	88.9
5c. Resource implications	5.6	0	0	11.1	16.7	61.1	27.8	5.6	0	33.3	0	5.6	5.6	5.6	11.1	22.2	72.2	0	77.8	11.1	5.6	77.8
5d. Monitor/audit criteria	61.1	22.2	66.7	72.2	55.6	61.1	83.3	50.0	66.7	77.8	55.6	61.1	44.4	44.4	50.0	72.2	83.3	61.1	66.7	27.8	50.0	77.8
6. Editorial independence:	83.3	75.0	69.4	**100**	66.7	**100**	**100**	50.0	75.0	50.0	27.8	66.7	66.7	**100**	**100**	50.0	**100**	50.0	80.6	0	**100**	**100**
6a. Funding body	66.7	100	100	100	66.7	100	100	100	100	100	55.6	66.7	66.7	100	100	0	100	0	100	0	100	100
6b. Competing interests	100	50.0	38.9	100	66.7	100	100	0	50.0	0	0	66.7	66.7	100	100	100	100	100	61.1	0	100	100
Overall Quality:	66.7	44.4	61.1	88.9	61.1	72.2	72.2	61.1	61.1	72.2	44.4	72.2	61.1	55.6	66.7	27.8	83.3	61.1	61.1	27.8	66.7	**94.4**
Recommendations:																						
a. Not recommended	0	**100**	33.3	0	33.3	0	0	0	0	0	33.3	0	0	33.3	0	0	0	0	0	33.3	0	0
b. Recommended with modifications	0	0	33.3	0	66.6	66.6	33.3	33.3	33.3	0	0	0	33.3	66.6	33.3	**100**	0	100	**100**	66.6	0	0
c. Recommended without modifications	**100**	0	33.3	**100**	0	33.3	66.6	66.6	66.6	**100**	66.6	**100**	66.6	0	66.6	0	**100**	0	0	0	**100**	**100**

Figure 1. Detailed AGREE II scores of CPGs for the nutritional management of patients with CF (% of maximum scoring for each domain and subcategory). Highest scoring in each category is presented in bold font. ADA, American Diabetes Association; AGREE, Appraisal of Guidelines, Research and Evaluation; CFF, Cystic Fibrosis Foundation; CFT, Cystic Foundation Trust; CPGs, Clinical Practice Guidelines; DAA, Dietitians Association of Australia; ECFS, European Cystic Fibrosis Society; ESPEN, European Society of Clinical nutrition and Metabolism; ESPGHAN, European Society for Pediatric, Gastroenterology Hepatology and Nutrition; ISPAD, International Society for Pediatric and Adolescent Diabetes; NASPGHAN, North America Society for Pediatric, Gastroenterology Hepatology and Nutrition; NICE, National Institute for Health and Care Excellence; PES, Pediatric Endocrine Society; PGS, Paediatric Gastroenterology Society; SBPT, Sociedade Brasileira de Pneumologia e Tisiologia; TSANZ, Thoracic Society of Australia and New Zealand.

Recommendation:	CFF [34]	CFF [30]	CFF [32]	CFF [33]	CFF [31]	CFF/NASPGHAN [38]	CFT [39]
Dietitian involvement:			√				√
Nutritional Screening:		√					√
Routine Screening:		√					√
Nutritional Education:			√		√		√
Energy Intake:		110–200% of EI for the general population if >2 yrs old			90–110 kcal/kg/d		110–200% of general population target EI
Protein Intake:					2–3 yr: ≥13 g/d; 4–5 yr: ≥19 g/d; 2–5 yr at high nutritional risk: 110–120% EI, with increments of 10–20% until 200%		
Fat Intake:						35–40% of EI	
Vitamin A (IU/d):			ONS post-diagnosis				<1 yr: <1500 >1 yr: 1500–10,000
Vitamin D (IU/d):			ONS post-diagnosis	<1 yr: 400–500 vit D_3; 1-10 yrs: 800–1000 vit D_3; >10 yrs: 800–2000 vit D_3; If serum 25(OH)D >20 ng/ml (≥50 nmol/L) but <30 ng/mL (<75 nmol/L) with confirmed adherence to prescribed regimen, ↑ vit D_3 dose to 800–1000, 1600–3000 and 1600–6000, respectively. All patients must be treated with vit D_3 ONS to maintain 25(OH)D >30 ng/mL			<1 yr: 400–2000 >1 yr: 400–5000
Vitamin D Prescription:			ONS post-diagnosis	Vit D_3 prescription (additional to other ONS) on a once/day dose, or weekly eq, to maintain 25(OH)D >30 ng/m			
Vitamin E (IU/d):			ONS post-diagnosis				<1 yr: 4—80 1–3 yr: 50–150 4–7 yr: 150–300 8–18 yr: 150–500 Adults: 150–500
Vitamin K (mg/d):			ONS post-diagnosis				<2 yr: 0.3/kg rounded to nearest mg 2–7 yr: 5 >7 yr: 5–10
Sodium (Na):			<2 yrs: 1/8 ts table salt/d at diagnosis, ↑ to ¼ ts of table salt/d at 6 mo old				<1 yr: 1–2 mmol/kg, or <500 mg >1 yr: < 4 g in equal doses Adolescents/adults: <6 g in divided doses
Zinc (Zn) (mg/kg/d):			<2 yr: 1 in divided doses for a 6 mo period, for infants not adequately growing despite EI and PERT		1 (<25 mg/kg/d)		
PERT (LU/kg/meal):	<4 yrs: 1000 >4 yrs: 500 Doses 2500–6000: unclear safety, use with caution, only if effective by 3-d-fecal fat assay with improved absorption coefficient	500–2500	In infants initiate when: • 2 CFTR mutations associated with PI • Faecal elastase < 200 mg/g or CFA < 85% (when <6 mo old), or other PI evidence • Signs/symptoms of malabsorption (while awaiting other test results)				
PERT UL:	Doses >6000 LU/kg/meal associated with colonic strictures in children <12 yr old, irrespective of enzyme strength	<10,000 LU/kg/d, or <4000 LU/g dietary fat/d	Start at 2000–5000 LU/feed up to <2500 LU/kg/feeding to 10,000 LU/kg/d		<10,000 LU/kg/d		<10,000 LU/kg/d
PERT formula:			Generic, non-proprietary				
Oral Feeding:			<2 yr: human milk as the initial feed Use ↑ energy feeds in BW loss or inadequate gain				
Milk formula type:			Non-hydrolyzed protein				
ONS:			<2 yr: MV				
Linoleic acid:			Lack of evidence				
DHA:			Lack of evidence				
Fluoride (F):			Supplement water with F (0.25 mg/dL), if concentration <0.3 ppm				

Figure 2. Overview of nutrition recommendations for CF management (part a). BW, Body weight; CF, Cystic Fibrosis; CFA, coefficient of fat absorption; CFF, Cystic Fibrosis Foundation; CFT, Cystic Fibrosis Trust; CFTR, Cystic fibrosis transmembrane conductance regulator; DHA, docosahexaenoic acid; eq, equivalent; EI, Energy Intake; F, Fluorine; LU, Lipase Units; MV, Multivitamin; NASPGHAN, North America Society for Pediatric Gastroenterology Hepatology and Nutrition; ONS, Oral Nutrient Supplements; PI, Pancreatic Insufficiency; PERT, Pancreatic Enzyme Replacement Therapy; ts, teaspoon; UL, Upper Level; 25(OH)D, 25-hydroxy vitamin D; ↑, increase/high.

Recommendations:	ADA/CFF/PES [37]	ECFS [25,28]	ECFS (for LTX) [26]	ECFS (gestation) [29]	ESPEN/ESPGHAN/ ECFS [23]	ISPAD [41]	NICE [40]	PGS/DAA [42]	SBPT [43]	TSANZ [22]
Dietitian involvement:		√		√			√	√	√	√
Nutritional Screening:	√	√		√	√		√	√	√	√
Routine Screening:	√	√					√		√	√
Nutrition Education:					√			√		√
Nutritional Status:		<2 yrs: BW & height PC* >2 yrs: achieve 50th PC for BMI Growth targets must reflect genetic potential, sibling height and local demographics* Adult: BMI >20 kg/m², ♀: 22 kg/m², ♂: 23 kg/m²								
Energy Intake (EI):	120–150% of DRI; individualized based on BW and growth. No restriction in gestation/ IGT	120–150% of EI. If poor BW gain persists despite optimal PERT, other causes of poor growth/malabsorption must be evaluated	Based on the recommendations for other surgical/ transplant patients. Correct low BMI and promote healthy BW before LTX	↑-energy density. Optimize energy in adolescent/multiple gestation. If nutritional status/ BMI cannot be optimized by ↑-energy-diet, resort to ONS or more invasive support.	110–200% of the general population target EI	>120–150% of normal EI for age/gender. Restriction only for older, overweight with mild mutations	↑ EI by portion size and ↑-energy foods, if concerned for BW loss		110–200% of recommended EI for age/sex	110–200% of general population EI
Protein Intake:			Based on advice for general surgery and transplant patients			200% of RNI in non-CF				15–20% of EI
Fat Intake:	35–40% of EI; no restriction on type of fat					40% of EI			35–40% of EI	100 g/d if >5 yrs
Carbohydrate Intake:	Individualized but monitored to achieve glycemic control. Avoid NNS					45–50% EI; avoid: sugary beverages				
Fiber Intake:			Provide adequate fluid and fiber intake and bowel movements should occur within 48–72 h post-surgery, or use laxatives/enemas			Encouraged in the well-nourished. In poorly nourished it may reduce EI				14–30 g/d
Vitamin A:		Monitor intake and status. ONS at <10,000 IU/d	Monitor possible hypervitaminosis		Achieve normal serum retinol range					ONS for all
b-carotene:		In CF with PI: 0.5–1 mg/kg/d								
Vitamin D:		Monitor levels and use ONS if low and in pancreatic sufficient women not taking ONS	Provide adequate Ca and vitamin D intake to avoid osteoporosis		ONS to maintain 25(OH)D >20 ng/mL. Safe sun exposure. Pregnancy: +600 IU/d					Inconsistent evidence for ONS
Vitamin E:			Monitor possible hypervitaminosis		ONS to maintain a-tocopherol/TC >5.4 mg/g					ONS in CF with PI
Vitamin K:					Infants: 0.3–1 mg/d Children/Adults: 1–10 mg/d					Routinely ONS in CF with PI
Sodium:	↑-salt intake especially in warm conditions and exercise	Families of breast-fed infants must be advised on salt intake and ONS. Consider NaCl ONS (2 mmol/kg/d) for all CF infants, increase in periods of hot weather or ↑ salt loss			0–6 mo: 1–2 mmol/kg/d Children/adults: Salty foods or NaCl caps/vials	↑ requirement: unrestricted intake				Infant: 0.5–1 g Child: 1–4 g Adolescent/ adult: 6 g
PERT:		Infants with PI should be commenced on PERT. Start at 2000 LU/100 mL standard formula and increase in malabsorption, or inadequate BW gain. ↑ doses (>10,000 LU/kg/d) must be monitored by an experienced CF dietician and/or a pediatric gastroenterologist.	Provide adequate PERT		<1 yr: 2000–4000 LU/120 mL formula/breast milk and 2000 LU/g fat in food 1-4 yrs: 2000–4000 LU/g dietary fat, ↑ as needed (until 10,000 LU/kg/d) >4 yrs & adult: Start at 500 LU/kg/meal, titrating until max dose		Offer PERT in exocrine PI. Adjust dose as needed to ↓ signs and symptoms of malabsorption	Infant: 500–1000 LU/g of dietary fat. Start with min dose (e.g. 2500 LU/ breast-feed or 120 mL formula). Children/Adult: 500–4000 LU/g fat Distribute dose in day based on fat intake		
PERT UL:					1000–2500 LU/kg/meal, or 10,000 LU/kg/d, or 2000–4000 LU/g diet fat			10,000 LU/kg/d. Aim for lowest effective dose	>10,000 LU/kg/d. May be needed in accelerated growth phases	
Oral Feeding:		0–1 yr: Breast feeding 2–5 yr: ↑-fat diet, based on growth and nutritional status > 5 yr: Typical adult ONS	Oral diet can usually resume on POD							
Milk Formula Type:		Preferably, ↑-energy density. Regular formula can be supplemented with CHO (10–12 g/0.1 L) and fat (5 g/0.1 L) until energy density of 1 kcal/mL. Encourage breast-feeding. No evidence for routine use of hydrolyzed formula, but may be used in non-CF malabsorption								
ONS:	CF-specific vitamins or MV	For extra EI in a short-term trial, or as meal when ill. No evidence supporting ONS of trace elements beyond the age-appropriate RDA.		Prescribed based on condition, BW and needs. Alternating flavor and type of ONS. FA: 400 µg/d precon-ceptionally and 1st trim, or 4–5 mg/d in ↑ risk.			If ↑ portion size and ↑-energy foods not effective, consider ONS			
Fat-soluble Vitamins:	ONS	Use routinely in infants with PI. No consensus on dose and mode of Vit K ONS	Monitor levels						Better absorbed with meals/PERT	
Appetite Stimulants:							Only short-term, for adults (<3 mo)			
Alcohol:	Beware of ↑ prevalence of liver disease			Advice on reducing intake						

Figure 3. Overview of nutrition recommendations for CF management (part b). ADA, American Diabetes Association; BMI, Body Mass Index; BW, body weight; Ca, Calcium; CHO, Carbohydrate; CF, Cystic Fibrosis; CFF, Cystic Fibrosis Foundation; DAA, Dietitians Association of Australia; DHA, docosahexaenoic acid; DRI, Dietary Reference Intake; ECFS, European Cystic Fibrosis Society; EI, Energy Intake; ESPEN, European Society for Clinical Nutrition and Metabolism; ESPGHAN, European Society for Pediatric Gastroenterology, Hepatology and Nutrition; FA, folic acid; GI, Gastrointestinal; IGT, Impaired glucose tolerance; ISPAD, International Society for Pediatric and Adolescent Diabetes; IU, International Units; LTX, lung transplantation; LU, Lipase units; MNT, medical nutrition therapy; MV, multi-vitamin; NaCl, Sodium chloride; NASPGHAN, North America Society for Pediatric Gastroenterology, Hepatology and Nutrition; NNS, non-nutritive sweeteners; NICE, National Institute for Health and Care Excellence; ONS, Oral Nutrient Supplements; PC, Percentiles; PI, Pancreatic Insufficiency; PERT, Pancreatic Enzyme Replacement Therapy; PES, Pediatric Endocrine Society; PGS, Pediatric Gastroenterology Society; POD, post-operative day; RDA, Recommended daily intake; RNI, Recommended nutrient intake; SBPT, Sociedade Brasileira de Pneumologia e Tisiologia; TC, Total cholesterol; TSANZ, Thoracic Society of Australia and New Zealand; UL, Upper level; 25(OH)D, 25-hydroxy vitamin D; ↑, increased/high; ↓, reduced/low; * similar to non-CF.

Distinct recommendations were made for different micronutrients, including fat-soluble vitamins (A, D, E, and K), Zinc, and Sodium intake. The intake of Zn is recommended for infants with inadequate growth only [32], whereas adequate Na or salt intake is highlighted by most CPGs, due to increased losses, especially during warm weather conditions and exercise.

With regard to the oral nutrient supplementation (ONS), multi-vitamin (MV) supplements can be prescribed on an individual basis according to the condition, body weight (BW) gain, and personalized needs [29], or when *per os* intake does not appear to promote growth adequately [40]. However, patients should be monitored frequently, especially with regard to the fat-soluble vitamin levels.

3.3.3. Pancreatic Enzyme Replacement Therapy (PERT)

Most of the CPGs provided recommendations regarding PERT, the upper level (UL), formulas, and the ideal dosage in lipase units (LU) and delivery. The UL appears to be estimated at 10,000 LU/kg/day by most CPGs' panels, although higher doses might be required in accelerated growth phases [43].

3.3.4. Oral Feeding and Formula Type

Breast-feeding should be the initial feed received by the infant [32]. If a milk formula is selected, a high-energy-density formula should be preferred. However, even regular formula can be supplemented with additional carbohydrates (10–12 g/0.1 L) and fats (5 g/0.1 L), until reaching an energy density of 1 kcal/mL of prepared formula [25,28].

3.3.5. Other Issues of Nutritional Concern

According to the NICE [40], appetite stimulants should only be used among adult patients, for a short period of time (<3 months). The intake of alcohol should be reduced, and the high prevalence of liver disease in patients with a CF diagnosis must be highlighted from health care professionals [37].

3.3.6. Provision of EN and PN

Figure 4 outlines the recommendations regarding the enteral and parenteral nutrition (EN and PN, respectively) included in the CPGs, according to the condition of patients targeted in each CPG. Indications for the use of PN include a short-term provision [24], in severely ill patients or after major gastro-intestinal surgery [24], when the digestive track cannot be used [43] or when EN fails [25].

	CFF/NASPGHAN [38]	CFT [39]	CFF [35]	ECFS [24]	ECFS [25]	ECFS [29]	ESPEN/ ESPGHAN/ ECFS [23]	NICE [40]	SBPT [43]	ECFS [26]
CPGs scope:	Pediatric CF care	Nutrition in CF	EN for CF	Nutrition in CF	Best practice for CF	Gestation in CF	Nutrition in CF	CF management & diagnosis	CF treatment & diagnosis	LTX
EN:	If ONS fails to ↑ BW	In deteriorating nutritional status post routine care and ONS	Early introduction as a treatment option allows patient and family to become comfortable. Previous poor adherence is not an absolute contraindication to EN tube placement. Consider financial burden. Supplemental EN for pregnant/ lactating women with CF who cannot meet calories/protein goals		In severe malnutrition	May be used to improve weight gain and nutritional status. If required prior to conception it may prove difficult to achieve the ↑ pregnancy requirements	When oral interventions fail to achieve growth and nutritional status	If attempts to ↑ EI are not effective	For severe cases and short durations	Supplementary EN must start when oral intake is insufficient or if patient is unable to initiate an oral diet by POD 3–4, or if longer-term ventilation is required
Feeding Tube:	NG tube/GT, based on patient's preference	NG tube or GT	NG avoids the risk of surgery and is easily reversible. May be suitable for short-term rehabilitation during acute illness or as a trial of feeding tolerance prior to GT placement. Suitable for short-term (< 3 mo) feeding but may not be suitable for those requiring an indefinite period of supplemental feed. Screen for contraindications for GT placement. Percutaneous or surgical EN feeding tube is not recommended in acute illness.	NG tube/GT, based on patient's preference	NG tube/ GT				GT for long-term therapy	GT might reduce the use of EN feed, as oral intake increases and nutritional status ameliorates
EN mode:			In those intolerant to gastric feeding, jejunal feeding is suggested. Nocturnal infusion for those on supplemental EN							
Delivery regimen:			Overnight continuous feeds for daytime oral intake. Intermittent bolus feeds to replace meals. Bolus feeds after meals, when oral intake is inadequate							
EN Formula(s):			Standard, polymeric age-appropriate formula. Energy-dense (1.5–2.0 kcal/mL) when >1 yr old. Semi-elemental, age-appropriate formula. Home-prepared or blenderized formula.	Normally, ↑energy, non-elemental. Individual patients may benefit by elemental/MCT						
EN cessation:										only when a BMI >19 kg/m² has been achieved and maintained for 3–6 mo without supplementary nutrition
PERT:			-Orally before bolus/continuous EN -Orally after continuous EN -Orally mid-continuous EN Inline cartridge delivery system use for EN Dose: 1000–4000 LU/g fat (mean 1800 LU/g fat) Meal dose: 500–2500 LU/kg/meal							
PN:				Total PN only for short-term, post major (GI) surgery and in the severely ill	Only if EN is not possible or fails				When digestive tract cannot be used, or in SBS	
Monitor:			Growth/BMI, EN tolerance, development of disordered eating, oral aversion or other behavioral concerns during EN feeding							
Monitoring frequency:			At least annually							

Figure 4. Enteral (EN) and parenteral nutrition (PN) recommendations among included CPGs. BMI, body mass index; BW, body weight; CF, Cystic Fibrosis; CFF, Cystic Fibrosis Foundation; CFT, Cystic Fibrosis Trust; CPGs, Clinical practice guidelines; EI, Energy intake; EN, Enteral nutrition; ESPEN European Society for Clinical Nutrition and Metabolism; ESPGHAN, European Society for Pediatric Gastroenterology, Hepatology and Nutrition; ECFS, European Cystic Fibrosis Society; GI, gastrointestinal; GT, gastrostomy; LTX, Lung transplantation; LU, lipase units; MCT, medium-chain triglycerides; NG, nasogastric; NASPGHAN, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; NICE, National Institute for Health and Care Excellence; PERT, Pancreatic Enzyme Replacement Therapy; ONS, Oral nutrient supplement; PERT, Pancreatic enzyme replacement therapy; PN, parenteral nutrition; POD, post-operative day; SBS, short-bowel syndrome; SBPT, Sociedade Brasileira de Pneumologia e Tisiologia; ↑, increased/high.

4. Discussion

The present study revealed that many CF-CPGs incorporate MNT information, while seven have CF-MNT as their main aim. Despite the plethora of CPGs, their quality was suboptimal with many methodological limitations identified based on the AGREE, resulting in several CPGs not being suggested for use by the review panel. On the other hand, specific AGREE domains were substantially fulfilled by few CPGs, and few guidelines were recommended without modifications. The highest quality was demonstrated by the TSANZ [22] CPGs, whereas the lowest score was received by the PGS/DAA [42] CPGs, based on the AGREE II scoring system.

The aim of CF-MNT is to maintain growth, well-being, and overall health, limiting symptoms of the disease, while being constantly adapted to either preserve or ameliorate nutritional state [44]. It has been suggested that the aim and purpose of CPGs must be clear and precise, declared early on at the beginning of the document. As such, objectives were clearer in the SBPT [43] and TSANZ [22] CPGs, specific research questions were stressed by the majority of appraised guidelines [22,23,30–32,43,45], and target population was defined by many [22,23,30,32,38,39].

On the other hand, stakeholder involvement was adequately reported only by the CFF [30], including the multidisciplinary formation of group membership and the inclusion of target populations' preferences and views, as well as the inclusion of target users' (i.e., patients') involvement. As per patient involvement in particular, with studies indicating a low CPG adherence rate globally [14,46], the need for more patient-centered and patient-involved CF care, becomes evident. Additionally, with dietitians playing an important role in preventing and treating malnutrition, and subsequently disease progression in patients with CF [47], the involvement of dietitians in CF guidelines should not be neglected.

Methodological rigor of development is of great importance in CPGs, as it ensures that recommendations are reliable for decision making [48]. As such, the methodology behind each recommendation suggested should be clearly defined to minimize bias and increase rigor [49]. In the rigor domain, once again the TSANZ [22] CPG received the highest score, accounting for adequate search methods' definition, grading of evidence criteria, formulation of each recommendation based on the available evidence, and consideration of benefits and harms, while using an external review panel for the evidence analysis and setting a specific update date for the CPGs. The rigor domain revealed several inadequacies in the majority of CF-specific CPGs, with many lacking an external review panel [24,25,42], some underreporting the search methods [24,25,34,38], and few lacking a grading evidence protocol [24,34,39].

Recommendations need to be clear, precise, and unambiguous, as in the case of the CFF [31] and SBPT [43]. Key recommendations, in particular, must be identifiable in the text and management options must be suggested for improved implementation. Furthermore, recommendations must be applicable, with their applicability being facilitated by several tools and audit criteria. It has been suggested that healthcare professionals make better clinical decisions when sound clinical or health policy decisions are facilitated by tools to monitor and implement progress and outcomes. For example, according to healthcare professionals from Spain [50], computer-integrated CPGs might increase physician adherence, whereas in Taiwan [51], positive attitudes were recorded towards computerized CPGs. Overall, more attention is needed on integrating CPGs into everyday practice [52]; however, in the CPGs appraised herein, many were lacking the implementation of tools to facilitate physician adherence [24,30,31,38].

Finally, as far as editorial independence is concerned, the majority of CPGs reported a funding body, with only two lacking relevant information [25,42]. Additionally, competing interests were declared from experts included in the majority of the reviewed CPGs, except from the CFT [39], the ECFS [24], and the PGS/DAA [42]. According to Mozaffarian and Forouhi [53], vested interests tend to influence research priorities and, thus, affect results' interpretation and relevant recommendations. This is why editorial indepen-

dence, including conflicts of interest disclosure and declaration of funding, is pivotal in CPGs' development.

Among all included CPGs, the TSANZ [22] demonstrated the highest overall quality, being followed by the CFF [32] and the ESPEN/ESPGHAN/ECFS [23] ones. Additionally, five CPGs were suggested for implementation by healthcare professionals without modifications [22,23,32,39,43], and one was not recommended at all [34], probably due to outdated methodology and lack of rigor.

Figures 2–4 detail individual recommendations for the MNT of patients with CF. According to recent research [44], CF-MNT must be redefined according to age, pancreatic function, and disease stage. As observed by reading the overview tables, the majority of recommendations are age specific, with distinct recommendations being suggested for patients with pancreatic insufficiency. Overall, differences were observed regarding the need for oral nutrient supplementation (ONS), with few nutrients being suggested by some authorities for ONS, while other advising bodies consider the existing evidence as insufficient. Surprisingly, a dietitian is not deemed necessary for CF care in many CPGs, while the need for nutritional assessment and routine screening is also lacking greatly. As Hollander noted [54], with nutrient needs changing dramatically during the disease progress, nutritional care should be personalized and provided by a specialized CF dietitian. Moreover, research has shown that pediatric patients with CF, in particular, are prone to malnutrition [55], often under-consuming several nutrients [56].

As far as energy is concerned, given the reported malnutrition among patients with CF, a more liberal energy consumption is recommended by the majority of CPGs, whereas others suggest enteral nutrition and ONS as a means to manipulate energy intake in cases of inadequate growth. With weight gain being strongly associated with energy and fat intake [57] and many parents relying on energy-dense, nutrient-poor foods to meet the caloric needs of their children [58], more emphasis should be given on the nutrient density of the consumed foods.

Overall, studies indicate that adult patients tend to demonstrate adequate nutrition literacy and confidence in attaining nutrition goals, whereas, as far as children and adolescents are concerned, they exhibit low knowledge scores [59]. In addition, home-based nutrition education programs have shown to be successful in ameliorating nutrition literacy, fat intake, and disease management [60,61]. However, nutrition education does not appear to be of pivotal importance for the majority of advising bodies associated with CF care.

One possible limitation of the present study stems from the exclusion of CPGs published in languages other than the English language. The review and appraisal of CF CPGs, however, is unique, while the focus on nutrition therapy is in accordance with the modern therapeutic approaches for adjuvant CF care.

Today, CPGs' adherence is considered a quality of care indicator, harmonizing disease outcomes, while minimizing treatment differences between patients of distinct geographic regions and of different socioeconomic status. According to recent research [62], a more uniform care of patients with CF is achieved when implementing clinical pathways for nutrition and lower airway inflammation issues. Based on a nationwide survey, adherence to the guidelines by Australian health professionals has resulted in ameliorated nutritional status among children with CF [63]. In parallel, interventions to increase the degree of adherence to the CF guidelines by patients have resulted in significant improvements regarding nutritional outcomes [64]. Additionally, studies have shown that healthcare professionals are often unaware of the existence of CF-specific CPGs [65]. CPGs' non-adherence leads to the application of fragmented and inconsistent practices, non-evidence-based clinical decisions, and health discrepancies, impacting the clinical and economic burden of the disease [14]. On the other hand, implementation of CF-related clinical pathways for nutrition and lower airway inflammation issues improves the quality of care, leading to a more uniform management of patients with CF [62].

5. Conclusions

In essence, the present study reviewed all existing CPGs on CF care, with a focus on MNT. Despite the existence of several CPGs, many appear outdated, lacking rigor, transparency, applicability, and efficiency, while incorporating systematic bias. Considering that CPGs' adherence is associated with better outcomes and the need for improving life expectancy in patients with CF, the development of CPGs of better quality is deemed necessary.

Author Contributions: Conceptualization, D.P.B., D.G.G., M.G.G. and X.T.; methodology, M.G.G., X.T., K.G. and M.P.N.; formal analysis, X.T.; investigation, M.G.G., X.T., M.P.N., A.P. and D.P.; resources, D.P.B., Z.D., G.M. and T.V.; data curation, X.T., M.G.G., O.A., A.P., K.G., G.M. and D.P.; writing—original draft preparation, M.G.G., Z.D., D.P.B., D.G.G. and T.V.; writing—review and editing, M.G.G., T.V., D.G.G., K.G., X.T., D.P., K.T., G.M., Z.D. and D.P.B.; visualization, M.G.G. and X.T.; supervision, D.P.B., Z.D. and D.G.G.; project administration, D.P.B. and M.G.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Ethical review and approval were waived for this study, as this is a meta-research study, lacking primary data.

Informed Consent Statement: Not applicable.

Data Availability Statement: All data are available upon request to the first author.

Conflicts of Interest: The authors declare no conflict of interest. G.M. is a scientific officer of the Hellenic Food Authority. The author alone is responsible for the content and views expressed in this publication and he does not necessarily represent the decisions, policy, or views of the Hellenic Food Authority.

References

1. Farrell, P.M.; White, T.B.; Ren, C.L.; Hempstead, S.E.; Accurso, F.; Derichs, N.; Howenstine, M.; McColley, S.A.; Rock, M.; Rosenfeld, M.; et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. *J. Pediatr.* **2017**, *181*, S4–S15.e1. [CrossRef] [PubMed]
2. Drumm, M.L.; Collins, F.S. Molecular biology of cystic fibrosis. *Mol. Genet. Med.* **1993**, *3*, 33–68.
3. Kerem, B.; Rommens, J.M.; Buchanan, J.A.; Markiewicz, D.; Cox, T.K.; Chakravarti, A.; Buchwald, M.; Tsui, L.C. Identification of the cystic fibrosis gene: Genetic analysis. *Science* **1989**, *245*, 1073–1080. [CrossRef]
4. Calella, P.; Valerio, G.; Brodlie, M.; Donini, L.M.; Siervo, M. Cystic fibrosis, body composition, and health outcomes: A systematic review. *Nutrition* **2018**, *55–56*, 131–139. [CrossRef] [PubMed]
5. Reilly, J.J.; Edwards, C.A.; Weaver, L.T. Malnutrition in children with cystic fibrosis: The energy-balance equation. *J. Pediatr. Gastroenterol. Nutr.* **1997**, *25*, 127–136. [CrossRef]
6. Zemel, B.S.; Jawad, A.F.; FitzSimmons, S.; Stallings, V.A. Longitudinal relationship among growth, nutritional status, and pulmonary function in children with cystic fibrosis: Analysis of the Cystic Fibrosis Foundation National CF Patient Registry. *J. Pediatr.* **2000**, *137*, 374–380. [CrossRef] [PubMed]
7. Bradley, G.M.; Blackman, S.M.; Watson, C.P.; Doshi, V.K.; Cutting, G.R. Genetic modifiers of nutritional status in cystic fibrosis. *Am. J. Clin. Nutr.* **2012**, *96*, 1299–1308. [CrossRef] [PubMed]
8. Hauschild, D.B.; Rosa, A.F.; Ventura, J.C.; Barbosa, E.; Moreira, E.A.M.; Ludwig Neto, N.; Moreno, Y.M.F.; Moreno, Y.M.F. Association of nutritional status with lung function and morbidity in children and adolescents with cystic fibrosis: A 36-month cohort study. *Rev. Paul. Pediatr.* **2018**, *36*, 8. [CrossRef] [PubMed]
9. Smyth, R.L.; Rayner, O. Oral calorie supplements for cystic fibrosis. *Cochrane Database Syst. Rev.* **2017**, *5*, CD000406. [CrossRef]
10. Poulimeneas, D.; Petrocheilou, A.; Grammatikopoulou, M.G.; Kaditis, A.G.; Loukou, I.; Doudounakis, S.E.; Laggas, D.; Vassilakou, T. High attainment of optimal nutritional and growth status observed among Greek pediatric cystic fibrosis patients: Results from the GreeCF study. *J. Pediatr. Endocrinol. Metab.* **2017**, *30*, 1169–1176. [CrossRef]
11. McNamara, J.J.; McColley, S.A.; Marigowda, G.; Liu, F.; Tian, S.; Owen, C.A.; Stiles, D.; Li, C.; Waltz, D.; Wang, L.T.; et al. Safety, pharmacokinetics, and pharmacodynamics of lumacaftor and ivacaftor combination therapy in children aged 2–5 years with cystic fibrosis homozygous for F508del-CFTR: An open-label phase 3 study. *Lancet Respir. Med.* **2019**, *7*, 325–335. [CrossRef]
12. McPhail, G.L.; Acton, J.D.; Fenchel, M.C.; Amin, R.S.; Seid, M. Improvements in Lung Function Outcomes in Children with Cystic Fibrosis are Associated with Better Nutrition, Fewer Chronic Pseudomonas aeruginosa Infections, and Dornase Alfa Use. *J. Pediatr.* **2008**, *153*, 752–757. [CrossRef]

13. Stephenson, A.L.; Mannik, L.A.; Walsh, S.; Brotherwood, M.; Robert, R.; Darling, P.B.; Nisenbaum, R.; Moerman, J.; Stanojevic, S. Longitudinal trends in nutritional status and the relation between lung function and BMI in cystic fibrosis: A population-based cohort study. *Am. J. Clin. Nutr.* **2013**, *97*, 872–877. [CrossRef] [PubMed]
14. Narayanan, S.; Mainz, J.G.; Gala, S.; Tabori, H.; Grossoehme, D. Adherence to therapies in cystic fibrosis: A targeted literature review. *Expert Rev. Respir. Med.* **2017**, *11*, 129–145. [CrossRef] [PubMed]
15. Madge, S.; Bell, S.C.; Burgel, P.-R.; De Rijcke, K.; Blasi, F.; Elborn, J.S. ERS/ECFS task force: The provision of care for adults with cystic fibrosis in Europe Limitations to providing adult cystic fibrosis care in Europe: Results of a care centre survey. *J. Cyst. Fibros.* **2017**, *16*, 85–88. [CrossRef] [PubMed]
16. Skolnik, K.; Quon, B.S. Recent advances in the understanding and management of cystic fibrosis pulmonary exacerbations. *F1000Research* **2018**, *7*, Faculty Rev-575. [CrossRef]
17. Methley, A.M.; Campbell, S.; Chew-Graham, C.; McNally, R.; Cheraghi-Sohi, S. PICO, PICOS and SPIDER: A comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv. Res.* **2014**, *14*, 579. [CrossRef]
18. Johnston, A.; Kelly, S.E.; Hsieh, S.-C.; Skidmore, B.; Wells, G.A. Systematic reviews of clinical practice guidelines: A methodological guide. *J. Clin. Epidemiol.* **2019**, *108*, 64–76. [CrossRef]
19. Brouwers, M.C.; Kho, M.E.; Browman, G.P.; Burgers, J.S.; Cluzeau, F.; Feder, G.; Fervers, B.; Graham, I.D.; Grimshaw, J.; Hanna, S.E.; et al. AGREE II: Advancing guideline development, reporting and evaluation in health care. *J. Clin. Epidemiol.* **2010**, *63*, 1308–1311. [CrossRef]
20. Brouwers, M.C.; Kerkvliet, K.; Spithoff, K.; AGREE Next Steps Consortium. The AGREE Reporting Checklist: A tool to improve reporting of clinical practice guidelines. *BMJ* **2016**, *352*, i1152. [CrossRef]
21. Grammatikopoulou, M.G.; Theodoridis, X.; Gkiouras, K.; Stamouli, E.-M.; Mavrantoni, M.-E.; Dardavessis, T.; Bogdanos, D.P. AGREEing on Guidelines for Nutrition Management of Adult Severe Burn Patients. *JPEN. J. Parenter. Enteral Nutr.* **2019**, *43*, 490–496. [CrossRef]
22. Saxby, N.; Painter, C.; Kench, A.; King, S.; Crowder, T.; van der Haak, N.; Australian and New Zealand Cystic Fibrosis Nutrition Guideline Authorship Group. *Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand*; CFA: Sydney, Australia; CFNZ: Sydney, Australia; TSANZ: Sydney, Australia, 2017.
23. Turck, D.; Braegger, C.P.; Colombo, C.; Declercq, D.; Morton, A.; Pancheva, R.; Robberecht, E.; Stern, M.; Strandvik, B.; Wolfe, S.; et al. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. *Clin. Nutr.* **2016**, *35*, 557–577. [CrossRef] [PubMed]
24. Sinaasappel, M.; Stern, M.; Littlewood, J.; Wolfe, S.; Steinkamp, G.; Heijerman, H.G.M.; Robberecht, E.; Döring, G. Nutrition in patients with cystic fibrosis: A European Consensus. *J. Cyst. Fibros.* **2002**, *1*, 51–75. [CrossRef]
25. Castellani, C.; Duff, A.J.A.; Bell, S.C.; Heijerman, H.G.M.; Munck, A.; Ratjen, F.; Sermet-Gaudelus, I.; Southern, K.W.; Barben, J.; Flume, P.A.; et al. ECFS best practice guidelines: The 2018 revision. *J. Cyst. Fibros.* **2018**, *17*, 153–178. [CrossRef]
26. Hirche, T.O.; Knoop, C.; Hebestreit, H.; Shimmin, D.; Solé, A.; Elborn, J.S.; Ellemunter, H.; Aurora, P.; Hogardt, M.; Wagner, T.O.F.; et al. Practical guidelines: Lung transplantation in patients with cystic fibrosis. *Pulm. Med.* **2014**, *2014*, 621342. [CrossRef]
27. Colombo, C.; Ellemunter, H.; Houwen, R.; Munck, A.; Taylor, C.; Wilschanski, M. Guidelines for the Diagnosis and Management of Distal Intestinal Obstruction Syndrome in Cystic Fibrosis Patients. *J. Cyst. Fibros.* **2011**, *10*, S24–S28. [CrossRef]
28. Sermet-Gaudelus, I.; Mayell, S.J.; Southern, K.W. Guidelines on the early management of infants diagnosed with cystic fibrosis following newborn screening. *J. Cyst. Fibros.* **2010**, *9*, 323–329. [CrossRef]
29. Edenborough, F.P.; Borgo, G.; Knoop, C.; Lannefors, L.; Mackenzie, W.E.; Madge, S.; Morton, A.M.; Oxley, H.C.; Touw, D.J.; Benham, M.; et al. Guidelines for the management of pregnancy in women with cystic fibrosis. *J. Cyst. Fibros.* **2008**, *7*, S2–S32. [CrossRef] [PubMed]
30. Stallings, V.A.; Stark, L.J.; Robinson, K.A.; Feranchak, A.P.; Quinton, H. Clinical Practice Guidelines on Growth and Nutrition Subcommittee; Ad Hoc Working Group Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency: Results of a Systematic Review. *J. Am. Diet. Assoc.* **2008**, *108*, 832–839. [CrossRef]
31. Lahiri, T.; Hempstead, S.E.; Brady, C.; Cannon, C.L.; Clark, K.; Condren, M.E.; Guill, M.F.; Guillerman, R.P.; Leone, C.G.; Maguiness, K.; et al. Clinical Practice Guidelines From the Cystic Fibrosis Foundation for Preschoolers With Cystic Fibrosis. *Pediatrics* **2016**, *137*, e20151784. [CrossRef]
32. Borowitz, D.; Robinson, K.A.; Rosenfeld, M.; Davis, S.D.; Sabadosa, K.A.; Spear, S.L.; Michel, S.H.; Parad, R.B.; White, T.B.; Farrell, P.M.; et al. Cystic Fibrosis Foundation Evidence-Based Guidelines for Management of Infants with Cystic Fibrosis. *J. Pediatr.* **2009**, *155*, S73–S93. [CrossRef]
33. Tangpricha, V.; Kelly, A.; Stephenson, A.; Maguiness, K.; Enders, J.; Robinson, K.A.; Marshall, B.C.; Borowitz, D. Cystic Fibrosis Foundation Vitamin D Evidence-Based Review Committee An update on the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis: Evidence-based recommendations from the Cystic Fibrosis Foundation. *J. Clin. Endocrinol. Metab.* **2012**, *97*, 1082–1093. [CrossRef] [PubMed]
34. Borowitz, D.S.; Grand, R.J.; Durie, P.R. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. Consensus Committee. *J. Pediatr.* **1995**, *127*, 681–684. [CrossRef]

35. Schwarzenberg, S.J.; Hempstead, S.E.; McDonald, C.M.; Powers, S.W.; Wooldridge, J.; Blair, S.; Freedman, S.; Harrington, E.; Murphy, P.J.; Palmer, L.; et al. Enteral tube feeding for individuals with cystic fibrosis: Cystic Fibrosis Foundation evidence-informed guidelines. *J. Cyst. Fibros.* **2016**, *15*, 724–735. [CrossRef] [PubMed]
36. Cystic Fibrosis Foundation, D.; Borowitz, D.; Parad, R.B.; Sharp, J.K.; Sabadosa, K.A.; Robinson, K.A.; Rock, M.J.; Farrell, P.M.; Sontag, M.K.; Rosenfeld, M.; et al. Cystic Fibrosis Foundation practice guidelines for the management of infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome during the first two years of life and beyond. *J. Pediatr.* **2009**, *155*, S106–S116. [CrossRef]
37. Moran, A.; Brunzell, C.; Cohen, R.C.; Katz, M.; Marshall, B.C.; Onady, G.; Robinson, K.A.; Sabadosa, K.A.; Stecenko, A.; Slovis, B.; et al. Clinical care guidelines for cystic fibrosis-related diabetes: A position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care* **2010**, *33*, 2697–2708. [CrossRef]
38. Borowitz, D.; Baker, R.D.; Stallings, V. Consensus report on nutrition for pediatric patients with cystic fibrosis. *J. Pediatr. Gastroenterol. Nutr.* **2002**, *35*, 246–259. [CrossRef]
39. Cystic Fibrosis Trust. *Nutritional Management of Cystic Fibrosis*; Cystic Fibrosis Trust: London, UK, 2016.
40. National Institute for Health and Care Excellence (NICE). *Cystic Fibrosis: Diagnosis and Management*; National Institute for Health and Care Excellence: London, UK, 2017.
41. Moran, A.; Pillay, K.; Becker, D.J.; Acerini, C.L. ISPAD Clinical Practice Consensus Guidelines 2014 Compendium Management of cystic fibrosis-related diabetes in children and adolescents. *Pediatr. Diabetes* **2014**, 65–76. [CrossRef]
42. Anthony, H.; Collins, C.E.; Davidson, G.; Mews, C.; Robinson, P.; Shepherd, R.; Stapleton, D. Pancreatic enzyme replacement therapy in cystic fibrosis: Australian guidelines. Pediatric Gastroenterological Society and the Dietitians Association of Australia. *J. Paediatr. Child Health* **1999**, *35*, 125–129. [CrossRef]
43. Athanazio, R.A.; da Silva Filho, L.V.R.F.; Vergara, A.A.; Ribeiro, A.F.; Riedi, C.A.; Procianoy, E.; Adde, F.V.; Reis, F.J.C.; Ribeiro, J.D.; Torres, L.A.; et al. Brazilian guidelines for the diagnosis and treatment of cystic fibrosis. *J. Bras. Pneumol.* **2017**, *43*, 219–245. [CrossRef]
44. Declercq, D.; Van Meerhaeghe, S.; Marchand, S.; Van Braeckel, E.; van Daele, S.; De Baets, F.; Van Biervliet, S. The nutritional status in CF: Being certain about the uncertainties. *Clin. Nutr. ESPEN* **2018**, *29*, 15–21. [CrossRef]
45. Simsek, H.; Meseri, R.; Sahin, S.; Ucku, R. Prevalence of food insecurity and malnutrition, factors related to malnutrition in the elderly: A community-based, cross-sectional study from Turkey. *Eur. Geriatr. Med.* **2013**, *4*, 226–230. [CrossRef]
46. Scheuing, N.; Berger, G.; Bergis, D.; Gohlke, B.; Konrad, K.; Laubner, K.; Lilienthal, E.; Moser, C.; Schütz-Fuhrmann, I.; Thon, A.; et al. Adherence to clinical care guidelines for cystic fibrosis-related diabetes in 659 German/Austrian patients. *J. Cyst. Fibros.* **2014**, *13*, 730–736. [CrossRef]
47. Rozga, M.; Handu, D. Nutrition Care for Patients with Cystic Fibrosis: An Evidence Analysis Center Scoping Review. *J. Acad. Nutr. Diet.* **2019**, *119*, 137–151.e1. [CrossRef] [PubMed]
48. Hoffmann-Eßer, W.; Siering, U.; Neugebauer, E.A.M.; Brockhaus, A.C.; Lampert, U.; Eikermann, M. Guideline appraisal with AGREE II: Systematic review of the current evidence on how users handle the 2 overall assessments. *PLoS ONE* **2017**, *12*, e0174831. [CrossRef]
49. Bero, L. Developing reliable dietary guidelines. *BMJ* **2017**, *359*, j4845. [CrossRef]
50. Gené-Badia, J.; Gallo, P.; Caïs, J.; Sánchez, E.; Carrion, C.; Arroyo, L.; Aymerich, M. The use of clinical practice guidelines in primary care: Professional mindlines and control mechanisms. *Gac. Sanit.* **2016**, *30*, 345–351. [CrossRef]
51. Hsiao, J.-L.; Chen, R.-F. Critical factors influencing physicians' intention to use computerized clinical practice guidelines: An integrative model of activity theory and the technology acceptance model. *BMC Med. Inform. Decis. Mak.* **2016**, *16*, 3. [CrossRef] [PubMed]
52. Larson, E. Status of practice guidelines in the United States: CDC guidelines as an example. *Prev. Med.* **2003**, *36*, 519–524. [CrossRef]
53. Mozaffarian, D.; Forouhi, N.G. Dietary guidelines and health—is nutrition science up to the task? *BMJ* **2018**, *360*, k822. [CrossRef]
54. Hollander, F.M.; de Roos, N.M.; Heijerman, H.G.M. The optimal approach to nutrition and cystic fibrosis. *Curr. Opin. Pulm. Med.* **2017**, *23*, 556–561. [CrossRef] [PubMed]
55. Poulimeneas, D.; Grammatikopoulou, M.G.; Petrocheilou, A.; Kaditis, A.G.; Vassilakou, T. Triage for Malnutrition Risk among Pediatric and Adolescent Outpatients with Cystic Fibrosis, Using a Disease-Specific Tool. *Children* **2020**, *7*, 269. [CrossRef] [PubMed]
56. Poulimeneas, D.; Grammatikopoulou, M.G.; Devetzi, P.; Petrocheilou, A.; Kaditis, A.G.; Papamitsou, T.; Doudounakis, S.E.; Vassilakou, T. Adherence to dietary recommendations, nutrient intake adequacy and diet quality among pediatric cystic fibrosis patients: Results from the Greecf study. *Nutrients* **2020**, *12*, 3126. [CrossRef] [PubMed]
57. Sainath, N.N.; Schall, J.; Bertolaso, C.; McAnlis, C.; Stallings, V.A. Italian and North American dietary intake after ivacaftor treatment for Cystic Fibrosis Gating Mutations. *J. Cyst. Fibros.* **2019**, *18*, 135–143. [CrossRef]
58. Sutherland, R.; Katz, T.; Liu, V.; Quintano, J.; Brunner, R.; Tong, C.W.; Collins, C.E.; Ooi, C.Y. Dietary intake of energy-dense, nutrient-poor and nutrient-dense food sources in children with cystic fibrosis. *J. Cyst. Fibros.* **2018**, *17*, 804–810. [CrossRef]
59. Lonabaugh, K.P.; O'Neal, K.S.; McIntosh, H.; Condren, M. Cystic fibrosis-related education: Are we meeting patient and caregiver expectations? *Patient Educ. Couns.* **2018**, *101*, 1865–1870. [CrossRef]

60. Watson, H.; Bilton, D.; Truby, H. A Randomized Controlled Trial of a New Behavioral Home-Based Nutrition Education Program, "Eat Well with CF," in Adults with Cystic Fibrosis. *J. Am. Diet. Assoc.* **2008**, *108*, 847–852. [CrossRef]
61. Janicke, D.M.; Mitchell, M.J.; Quittner, A.L.; Piazza-Waggoner, C.; Stark, L.J. The Impact of Behavioral Intervention on Family Interactions at Mealtime in Pediatric Cystic Fibrosis. *Child. Health Care* **2008**, *37*, 49–66. [CrossRef]
62. Singh, S.B.; Shelton, A.U.; Greenberg, B.; Starner, T.D. Implementation of cystic fibrosis clinical pathways improved physician adherence to care guidelines. *Pediatr. Pulmonol.* **2017**, *52*, 175–181. [CrossRef]
63. Ruseckaite, R.; Pekin, N.; King, S.; Carr, E.; Ahern, S.; Oldroyd, J.; Earnest, A.; Wainwright, C.; Armstrong, D. Evaluating the impact of 2006 Australasian Clinical Practice Guidelines for nutrition in children with cystic fibrosis in Australia. *Respir. Med.* **2018**, *142*, 7–14. [CrossRef]
64. Savant, A.P.; Britton, L.J.; Petren, K.; McColley, S.A.; Gutierrez, H.H. Sustained improvement in nutritional outcomes at two paediatric cystic fibrosis centres after quality improvement collaboratives. *BMJ Qual. Saf.* **2014**, *23*, i81–i89. [CrossRef] [PubMed]
65. Garber, E.; Desai, M.; Zhou, J.; Alba, L.; Angst, D.; Cabana, M.; Saiman, L. CF Infection Control Study Consortium Barriers to adherence to cystic fibrosis infection control guidelines. *Pediatr. Pulmonol.* **2008**, *43*, 900–907. [CrossRef] [PubMed]