NHS
The Leeds Teaching Hospitals
NHS Trust

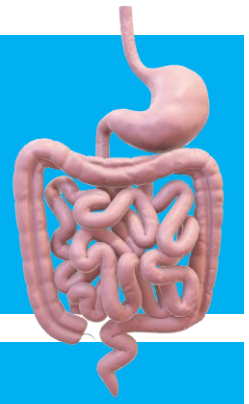

# Evolution of the nutritional management of children with CF

Jacqueline Lowdon
Leeds Children's Hospital, UK

# Outline

- First links with nutrition
- Progression from low fat to high fat dietary advice
- Good CF care & its links to nutrition
- Newborn Screening
- Development of Best Practice/Clinical Practice Guidelines
- Variant Specific Therapies

# First links with nutrition



- 1938 D. Andersen, likely caused by vitamin A deficiency
- Main presenting feature fat malabsorption & poor growth in infants & children
- But poor weight gain 2nd to lung disease & infections, rather than an independent contributor to morbidity & mortality
- Inevitable & relatively inconsequential in comparison to lung disease (Matthews et al 1964, Sproul et al 1964, Busey et al 1968)
- Today, achieving & maintaining optimal nutrition status is viewed as a critical component of CF care

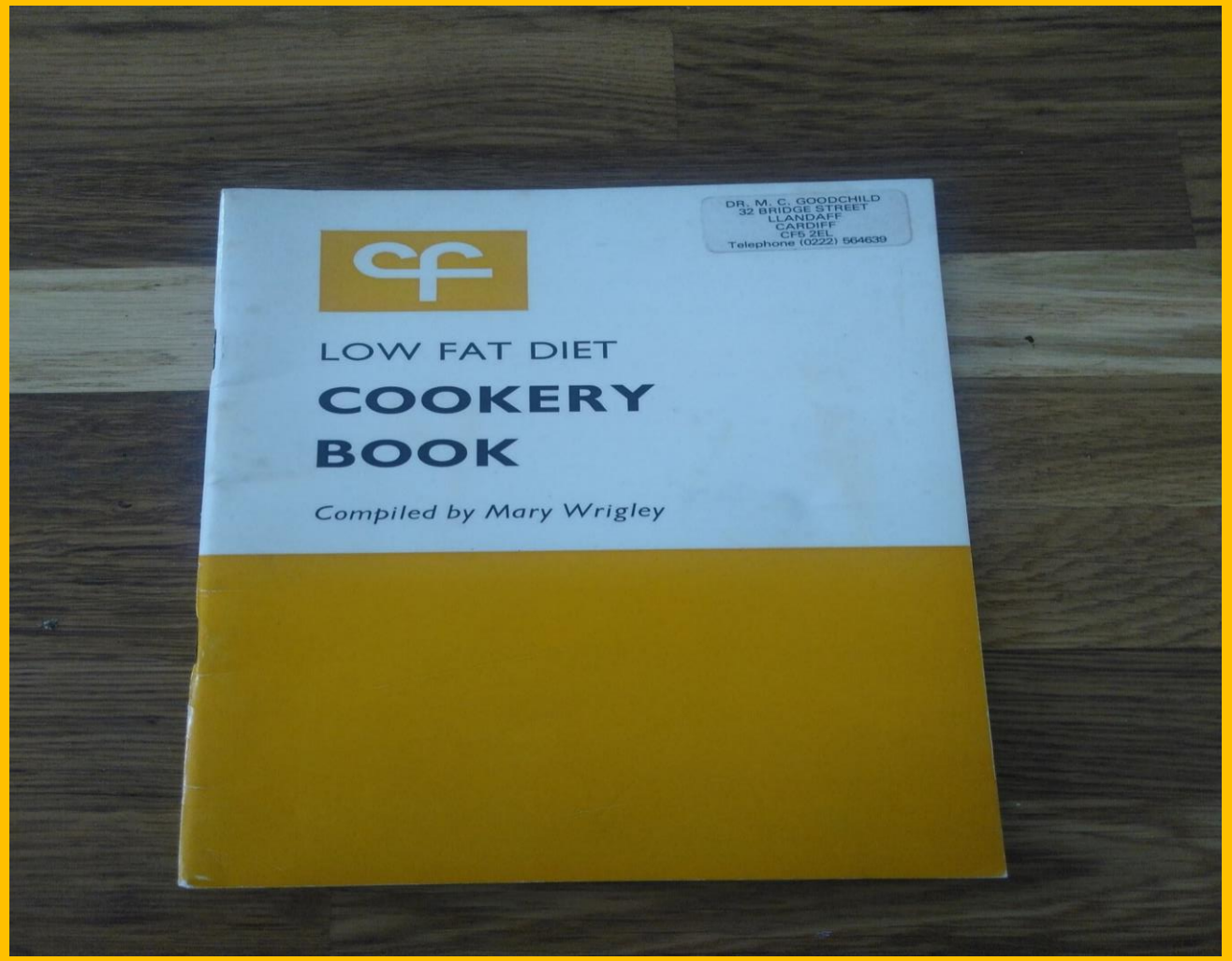
# Development of low fat dietary advice

- 1939 D. Andersen showed PERT improved intestinal malabsorption in CF
- **Chung AW et al. Studies in steatorrhoea. Effect of the level of dietary fat upon absorption of fat and other foodstuffs in idiopathic celiac disease and cystic fibrosis of the pancreas. Pediatrics 1951; 7:491-502**
- Demonstrated fat absorption was proportional to dietary intake BUT high fat intakes increased unpleasant GI symptoms
- Continue low fat diet
- Many could not tolerate a normal fat intake due to abdominal symptoms, even with large doses of PERT

# Development of hydrolysed feeds


- Fat-free diet of casein hydrolysate & glucose, nitrogen retention was normal & excretion normalized - hydrolysed casein could be used, in contrast to whole protein (Shohl et al. 1943)
- Absorption of whole protein & casein hydrolysate compared, suggested that substitution of the hydrolysate for whole protein would be of benefit (West et al. 1946)
- Feeds containing hydrolysed protein were shown to be useful in improving malabsorption, especially where control of malabsorption was difficult e.g. after MI operations
- Beef serum protein hydrolysate, glucose polymer & MCT fat (Allan et al 1973)

# Low Fat Cookery Book



# Enteric coated pancreatic enzymes

- Khaw KT, Adeniyi-Jones S, Gordon D, Polombo J, Suskind R. Efficacy of pancreatin preparations on fat and nitrogen absorptions in cystic fibrosis. Pediatr Res 1978; 12:437
- **Viokase & Cotazym, standard enzyme preparations, affected by gastric acid, Pancrease enteric coated**
- **12 children, 8-14 years**
- **Viokase 4/8/12 tablets, Cotazym 2/4/6 capsules and Pancrease 1/2/3 capsules/meal**
- **All 3 improved absorption but Pancrease did so at the smaller dose**
- **Repeatedly confirmed in subsequent controlled trials** (Gow et al 1981, Mischler et al 1982, Beverley et al 1987)

# Introduction of high fat diets

- **High fat diet first demonstrated improved growth** (Crozier et al 1974)
- **Boston low fat diet versus Toronto high fat diet**
- **Patients in Boston tended to be shorter than patients in Toronto**
- **Toronto males also weighed more than Boston males**
- **Independent of pulmonary function (no difference in FEV1)**
- **Median age of survival in Boston was 21 years, Toronto 30, showing a marked separation from age 10**
- **Resulted in a general recommendation of high-fat diet to patients with CF**
  Corey et al A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. J. Clin. Epidemiol. 1988;41:583–591. doi: 10.1016/0895-4356(88)90063-7

# Benefits of improved nutritional status

**Better nourished, better outcome** (Steinkamp & Wiedemann, 2002)

**Good growth & nutritional status early in life associated with better lung function during childhood** (Konstan et al 2003; , Peterson et al 2003, Pedreira et al 2005)

**Nutritional support improves nutritional status & stabilise/slow rate of lung function decline**
(Jelalian et al 1998, Walker & Gozal 1998, Steinkamp & Wiedemann 2002, Efrati et al 2006)

# European CF Conference 1997 (3rd Dietitians Meeting)

Lebecque P., Leonard A., De Boeck K. et al. (2009). Early referral to cystic fibrosis specialist centre impacts on respiratory outcome. J Cyst Fibros. Vol. 8, No 1, pp 26-30.

Twin sisters

Δ at 6 months of age

Low fat diet for 12 years

No PERT

No IV antibiotic courses

Took a year to adjust

Mum kept forgetting!

Felt angry/guilty/cried

"Gorging" = ½ bar chocolate at a time

Happy to gain weight BUT

Family had a non aggressive approach to their over all health

Due to their low expectations

Centralise & standardise patient care

Improves patient outcomes

# Good care management of CF: what does it look like?

Crozier D. (1974). Cystic fibrosis: a not-so-fatal disease. Pediatr Clin North Am. Vol. 21, No 4, pp 935-950

**Improved infrastructure –**

**CF centres, Networks**

**Intensive follow up**

Early diagnosis

Best Practice -

Benchmarking

CF registries

Guidelines

QI initiatives

Innovations

New therapies

Help – patients & parents/carers

Education

Resources

Support

# New Born Screening (NBS)

Farrelll et al. Evidence on improved outcomes with early diagnosis of CF through neonatal screening: enough is enough! J Ped 2005:147(3 Suppl): S30-6

- Start treatment early
- Prevent early decline in nutritional status
- Conserve respiratory function

# NBS in Wales, UK


- **Arch Dis Childh 1991;66:29-33**
- **1985-1989 infants, born in Wales & the West Midlands were randomized to CF NBS**
- **Has the potential to decrease infant CF deaths**
- **Pediatr Pulmonol 2001; 31:363-366**
- **NBS is of no advantage if the diagnosis is delayed & if they do not also receive CF centre care once diagnosed**

# CF Screen Positive Inconclusive Diagnosis/CF Transmembrane Conductance Regulator-related Metabolic Syndrome (CF SPID/CF CRMS)

- **Diagnosis of CF cannot be made or excluded with certainty**
- **Mainly asymptomatic**
- **Follow up required to detect those who will develop CF symptoms (10%)** Ren et al Outcomes of infants with indeterminate diagnosis detected by CF newborn screening. Pediatrics. 2015;135:e1386-e1392
- **Review at least annually for first 5 years**
- **Detailed assessment at 6 years of age, growth & pancreatic function** J Cyst Fibros. 2021 Sep;20(5):810-819. doi: 10.1016/j.jcf.2020.11.006. Epub 2020 Nov 27. Accessed May 2022.

# Nutrition & Growth in the early years

Early achievement of normal nutritional status is associated improvement in lung function in older childhood years (Stallings et al 2008, Lai et al 2009, Konstan 2003)

Wt for age percentile at 4 years associated with improved growth parameters during childhood & less pulmonary exacerbations at age 18 (Yen et al 2013)

# Nutrition & Growth in the early years

Returning to birth wt z score by 2 years is associated with improved linear growth & pulmonary function through to age 12 years
(Sanders et al 2018)

A height z score >C50% percentile at 6 years is associated with improved lung function
(Sanders et al 2021)

# Body Mass Index (BMI)

- **Epidemiological evidence that BMI is closely correlated with lung function & survival** (Stallings et al 2008)
- **European CF pt registry, lower BMI have a sixfold increased odds ratio of having severe lung disease compared to pts with a healthy BMI** (Kerem et al 2014)
- **Children with a BMI on or > C25th more likely to have better respiratory health** (Yen et al 2013, Stephenson et al 2013)
- **Evidence based nutrition goals, using BMI percentiles as outcomes, were then published**

# Best Practice/Clinical Practice Guidelines

- **ECFS, ESPEN/ESPGHAN/ECFS joint guidelines**
- **Australia & New Zealand Nutrition Guidelines**
- **Joint Pediatric Gastroenterological Society (PGS) & the Dietitians Association of Australia (DAA)**
- **UK CF Trust, National Institute for Health & Care Excellence (NICE)**
- **CF Foundation (CFF) & North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHN)**
- **International Society for Pediatric & Adolescent Diabetes (ISPAD)**
- **French CF Society**

# Best Practice/Clinical Practice Guidelines

- Grammatikopoulou 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/ children 8121180, accessed May 2022
- **Great variation in AGREE II domain-specific scores in all CPGs**
- **Suggests different strengths & weaknesses**
- **Outdated, lack rigor, transparency, applicability efficiency & biased**
- **As CPGs adherence is associated with better outcomes, the development of CPGs of better quality is deemed necessary**

# Pancreatic Enzyme Replacement Therapy (PERT)

- **Food supplement or drug ?**
- **Fibrosing Colonopathy (FC) & large PERT doses**
  (Smyth et al 1994, Smyth et 1995, Freiman & FitzSimmons et al 1996)
- **Thickening of submucous layer of the colon, occurs more in children**
- **Initially related to high strength pancreatic enzymes (HSPE)**
- **Epidemiological studies, strong link with a high dose, BUT**
- **Complications with a large dose of standard preparations** (Jones et al 1995)
- **US CFF/Food & Drug Admin 1995 detailed dosing instructions, removed HSPE, Not to exceed > 10 000IU lipase/kg/day**
- **CSM 1995 Not to exceed > 10 000IU lipase/kg/day, 15 years & under avoid HSPE, 3 brands of HSPE with methacrylic acid copolymer were removed (MAC)**

# Pancreatic Enzyme Replacement Therapy (PERT)

- **Disease was eradicated in the UK but US cases continued** (Stevens et al 2001)
- **All cases 40-50 000IU lipase/kg/day, all had MAC coated brands**
- **No FC case had ever exclusively received non MAC coated brand alone**
- **Doses of non MAC brands still exceeded dosing guidelines** (Mehta 2001)
- **FC cases without PERT** (Waters 1998, Mack et al 2004, Serban et al 2002)
- **FC associated with treatment with enteric-coated mesalazine pills** (Prieto et al 2002)
- **Since 1994, total enzyme doses have been reduced in most CF patients without any adverse effects on absorption, nutrition or growth**
  (Lowdon J, Goodchild MC, Ryley HC, Doull IJM. Maintenance of growth in cystic fibrosis despite reduction in pancreatic enzyme supplementation. Arch Dis Child 1998;78:377-8)

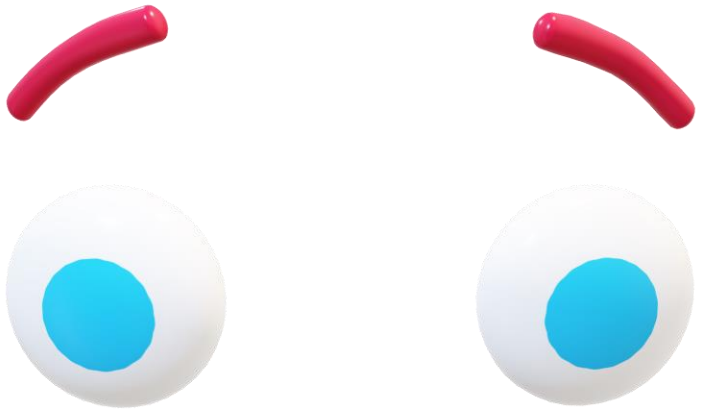
# CF Diabetes

- **Previously considered a disease of the older child & adult**
- **But can begin in early life** (Yi et al 2016, Hameed et al 2010, Prentice et al 2019)
- **During the 1990s, annual OGTT surveillance was just being established as the standard**
- **Screening & treatment CF diabetes most important changes in CF management** (Moran et al 2009)

# CF Bone Disease (CFBD)

- **Due to increased survival, new & unusual complications emerged, including low bone mineral density (BMD)**
- **2 studies in 1979 independently reported a decrease in BMD in CF compared with age-matched controls (Mischler et al 1979, Hahn et al 1979)**
- **Mid–late 1990's CFBD highlighted (Henderson et al 1994, Aris et al 1998, Haworth et al 1999)**
- **Risk factors highlighted & guidelines developed**
- **Preventive care is based on a multifaceted approach, including maintenance of good nutrition (Anabtawi et al 2019)**

# What’s next?



# Pancreatic Enzyme Replacement Therapy – new developments

- CFF with Synspira Therapeutics Inc. developing a **non-porcine PERT**
- Potential enzyme therapy SNSP003 contains 3 non-animal derived enzymes Feb 2020, additional funding Sept 2021
- 2017 U.S. Food & Drug Administration (FDA) approved **RELiZORB®,** digestive enzyme cartridge for 5-18 years who use a feeding tube
- Cartridge contains digestive enzymes, placed in line between the feed & the G-tube, allows for fats in the formula to be predigested
- Absorption and Safety With Sustained Use of RELiZORB Evaluation (ASSURE) Study in Patients With Cystic Fibrosis Receiving Enteral Feeding. Stevens et al. Journal of Pediatric Gastroenterology and Nutrition: October 2018 - Volume 67 - Issue 4 - p 527-532. doi: 10.1097/MPG.0000000000002110. Accessed May 2022

# Variant Specific Therapy (VST)





# UK Data

- People on VST as of December 2020:
- Kalydeco (Ivacaftor): 871
- Orkambi (Lumacaftor/ivacaftor): 1194
- Symkevi (Tezacaftor/ivacaftor): 1358
- Kaftrio (Elexacaftor/tezacaftor/ivacaftor): 2 700

# Weight & Growth with VST

- **Effect on anthropometric measurements is dependent on genetic mutation & modulator formulation** (Bailey et al 2020, Systematic review)
- **Increased weight & linear growth in children** (Stalvey et al 2017, Borowitz et al 2016, Davies et al 2013,)
- **Increased weight & BMI** (Rowe et al 2014, Davies et al 2016)
- **Proportion of overweight increased from 9% to 18% in children > 5.5 years** (Guimbellot et al 2021)
- **Rate of obesity remained stable in children but increased slightly from 8% to 11% in adults** (Guimbellot et al 2021)
- **Increase BMI in adolescents & adults on Kaftrio** (phase III clinical trials) (Middleton et al 2019, Heijerman et al 2019)

# Effects of Variant Specific Therapies: Reasons

- **Decreased resting energy expenditure**
- **Increased caloric intake**
- **Improved intestinal absorption**
- **All postulated to play a role in adults with gating mutations taking ivacaftor** (Stallings et al 2018)

- **REE decreased adults & children (5.5-12.0%, $p < 0.05$)** (Stallings et al 2018)
- **Patients are increasing fat & calorie intake significantly taking ivacaftor** (Sainath et al 2019)
- **Quantity of fat required for optimal drug efficacy is unknown**

# Pancreatic Function & Ivacaftor

- **Some evidence that children on ivacaftor have shown improvement, & for some, reversal of PI** (Rosenfeld 2019, Davies 2016, Gould 2021)
- **Early initiation of ivacaftor may reverse existing pancreatic damage & prevent or delay further damage in young children** (Rosenfeld 2019 et al, Davies 2016)

# CF Diabetes & VST (ivacaftor & orkambi)

- **VST, if initiated early, may protect endocrine & exocrine pancreas from inflammation & resultant destruction**
- **Some modest evidence that VST improve glucose abnormalities** (Bellin et al 2013, Hayes et al 2014, Tsabari et al 2016, Dagan et al 2017, Misgault et al 2020)
- **Longitudinal studies required, with glucose abnormalities as the primary outcome**
- **Will determine if it will treat, slow onset or prevent CF diabetes**
- The role of modulators in cystic fibrosis related diabetes Journal of Clinical & Translational Endocrinology Volume 27, March 2022, 100286

# CF Bone Disease & VST

- **Data suggestive that VST can:**
- **In mice, improve bone formation, mass & micro architecture** (Le Henaff et al 2014)
- **Human F508del osteoblasts improve underlying abnormalities** (Velard et al 2015, Sermet-Gaudelus et al 2016)
- **Retrospective study, 7 adults on ivacaftor for 1–3 year, significant improvement in lumbar spine BMD** (Sermet-Gaudelus et al 2016)
- **VST may have important clinical effects on lung function, nutritional status & physical activity levels & may further lead to improvement in bone density**

# Gut Microbiota & Intestinal Inflammation

- **GI tract is affected by significant alterations in diversity & composition of microbiota in PwCF vs healthy controls** (Manor et al 2016, Bruzzese et al 2014, Nielsen et al 2016)
- **As life expectancy increases, GI malignancy has increased** (Yamada et al 2018)
- **Chronic GI inflammation in CF begins in early childhood** (Garg et al 2018)
- **Probiotics significantly reduce faecal calprotectin in children & adults with CF**
- **Clinical implications require further investigation**
- **Multicentre RCTs of at least 12 months duration are required to assess efficacy & safety** (Probiotics for people with cystic fibrosis. Cochrane Database of Systematic Reviews. Coffey M, Garg M, Homaira N, Jaffe A, Ooi C. https://doi.org/10.1002/14651858.CD012949.pub2)

# Gut Microbiota & Intestinal Inflammation

- **Ivacaftor associated with:**
- **An increase in beneficial bacterial species (Akkermansia) & a decrease in calprotectin levels** (Ooi et al 2018)
- **Resolution of histopathological signs of intestinal inflammation in a case report** (Safe et al 2016)
- **Reduction in intestinal inflammation by ivacaftor was also associated with weight gain** (Stallings et al 2018)
- **To be determined in kaftrio** (Bass et al 2021)
- **Impact of VST in CF remains unclear**
  (Published online 2021 Aug 24. doi: 10.3390/nu13092907 The Impact of Highly Effective CFTR Modulators on Growth and Nutrition Status R. Bass, J. Brownell, V. Stallings. Accessed May 2022)

# Body Composition & VST

- Body composition is abnormal in individuals with CF (Sheikh et al 2014, Calella et al 2018)
- Prospective observational study PwCF 5–61 years increases in both fat-free mass & fat mass with ivacaftor (Stallings et al 2018)
- More studies of longer duration required, especially in the setting of unintended weight gain & development of overweight & obesity on VST

# Excess weight: is it always beneficial?

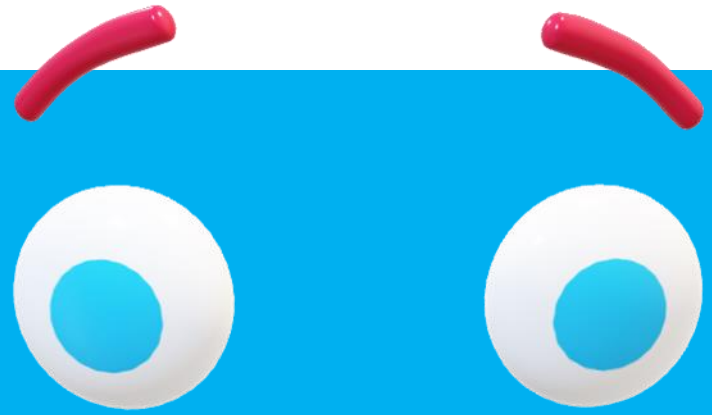
- **Dyslipidemia & insulin resistance have been observed in the CF population** (Kelly & Moran 2013, Worgall 2009)
- **How will these factors affect risk for development of heart disease & diabetes?**
- **How may obesity affect risk for development of co-morbidities ?**
  (Jiménez et al. Excess weight in patients with cystic fibrosis: Is it always beneficial? Nutr. Hosp. 2017, 34, 578)

# Overweight & Obesity

- **Emerging as an important issue in CF**
  (Stephenson et al 2013, Litvin et al 2019, Petersen et al 2021, Guimbellot et al 2021)
- **European CF Conference 2000 (6th Dietitians' Meeting)**
- **7 children, mean age 11.5 yrs (7.8-13.2) BMI>C95th**
- **Sex and age matched controls**
- **Comparable lung function & clinical scores, so did not protect from disease progression**
- **Posed several dilemmas for families & CF team**

# Diet Quality

- “CF Diet” – over reliance on energy dense, nutrient poor foods
- Studies of diet quality show high saturated fat, trans fat & total calories but low in nutrient-dense foods e.g. fruits and vegetables (McDonald et al Dietary Macronutrient Distribution and Nutrition Outcomes in Persons with Cystic Fibrosis: An Evidence Analysis Center Systematic Review. J. Acad. Nutr. Diet. 2021)
- Dietary fibre & the occurrence of gut symptoms in CF (Gavin et al 1997)
- Almost 50% had energy intakes below recommended & lower intakes were associated with sub-optimal body growth (Woestenenk et al 2019)
- For some, a high energy diet, at present, remains a key component



# Looking Forwards?

"The diet in Cystic Fibrosis is a very individual matter"

# Summary

- Significant strides have been made in CF treatment & outcomes
- Nutritional care is an important part of personalized care
- Dietitians play a critical role in helping to improve outcomes & QOL
- Nutritional management of CF is continuous & requires continued nutritional scientific research
- More experiences of VST & its effects on nutritional status will offer challenges to adapt dietary interventions in CF
- Aim is to achieve & maintain optimal nutrition status, ensuring that our patients will have the best chance at a long & relatively healthy life