OPTIMISING NUTRITION IN CF ADULTS

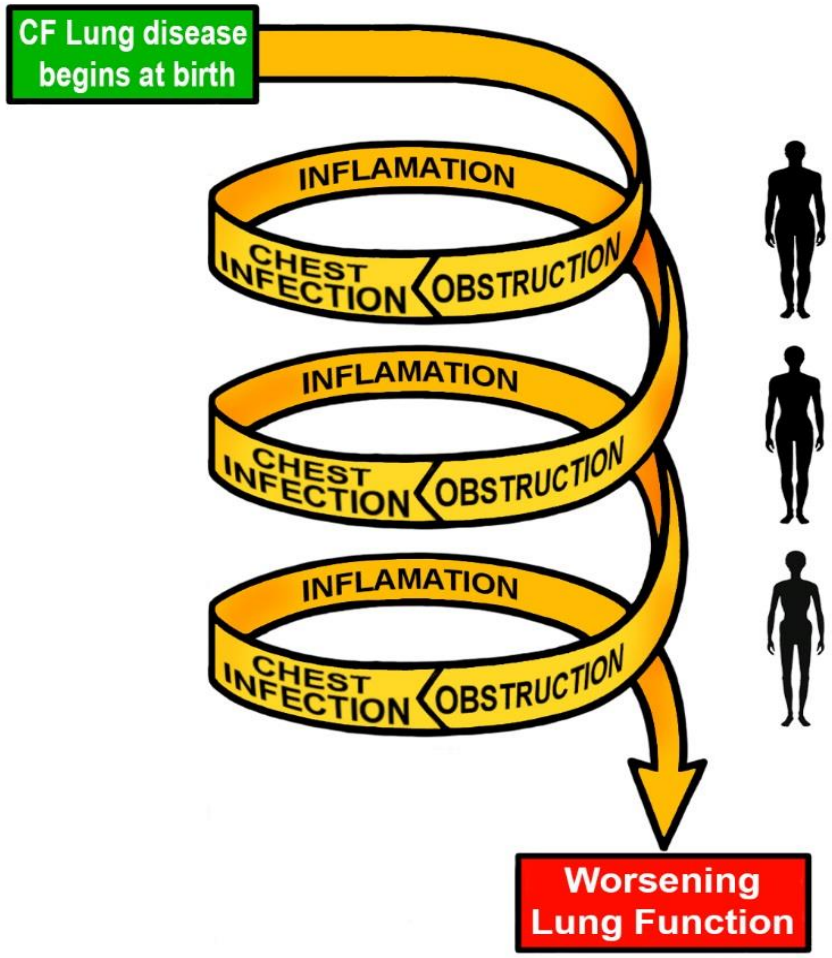
DR HELEN WHITE

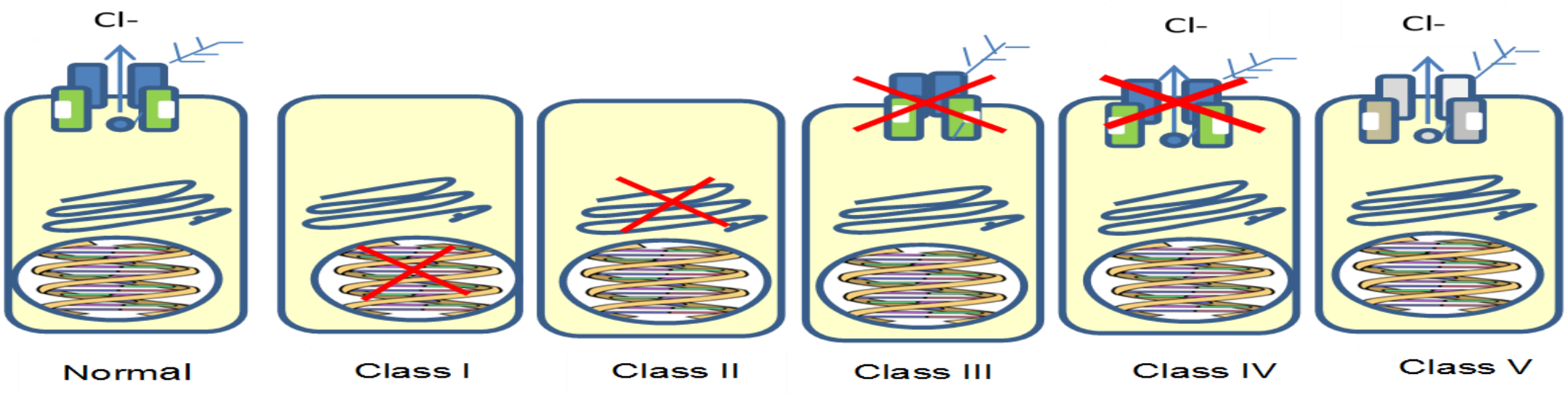
LEEDS BECKETT UNIVERSITY

MULTISYSTEM DISEASE

Pancreatic insufficiency	**Nutritional status CF related diabetes Fat soluble vitamin status Bone health**
Increased requirements	**Nutritional status**
CFTR	**Differing nutritional needs between Genotype**
CF Related liver disease	
Pregnancy	
Transplantation …	

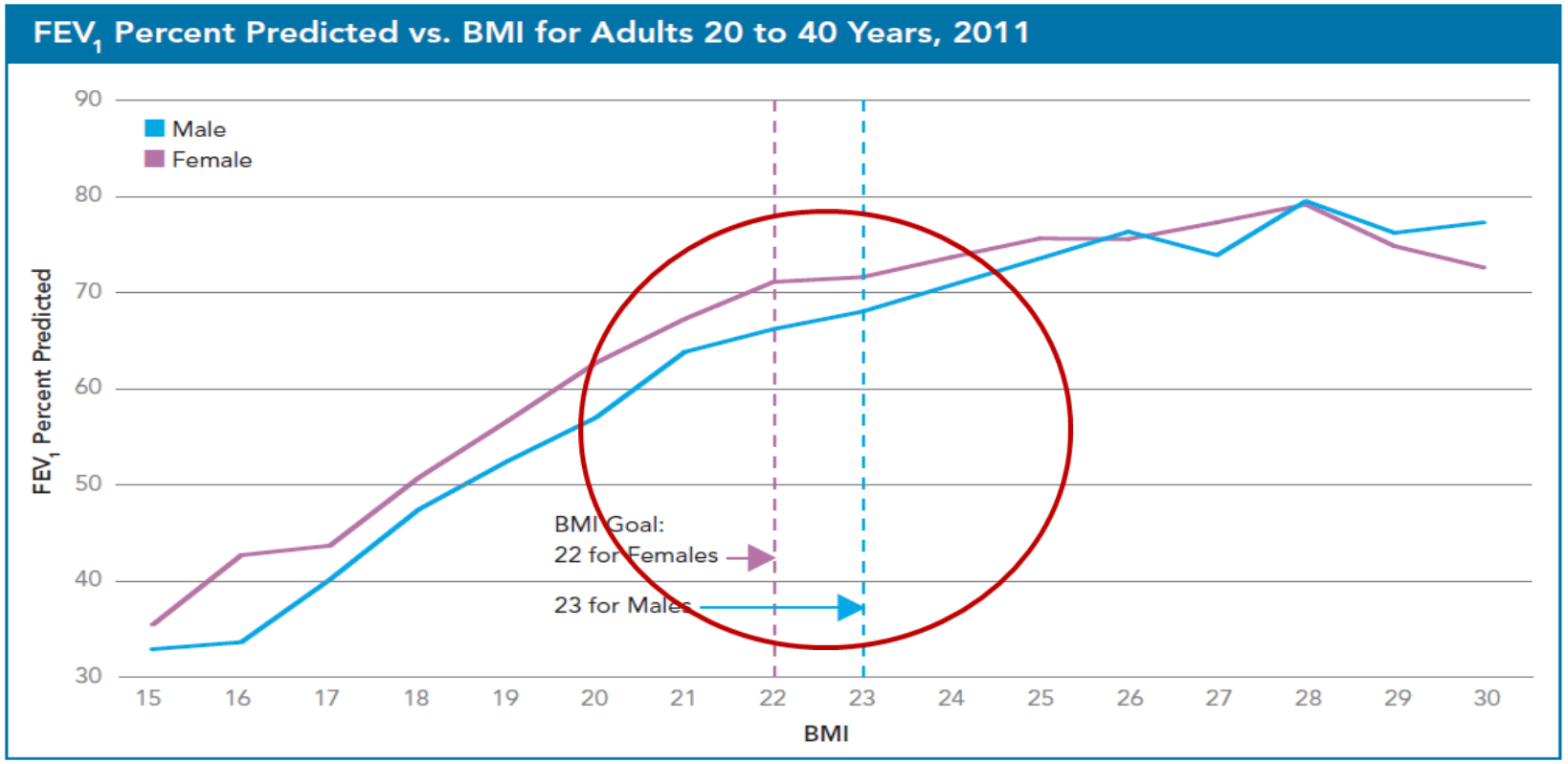
Greater complexity of care in adulthood





Class I mutations	CFTR production is stopped early and protein production becomes defective. Class 1 patients have no functioning CFTR chloride channels
Class II mutations	CFTR is is poorly processed and is destroyed within the cell, resulting in little or no CFTR reaching the cell surface
Class III mutations	CFTR reaches the cell surface but does not work, unable to open properly to transport chloride
Class IV mutations	CFTR reaches the apical surface but the defective conduction of chloride through the channel results in poor CFTR function
Class V mutations	Decreased production of CFTR results in some production, but insufficient to maintain normal function

REASONS FOR NEW TARGETS?

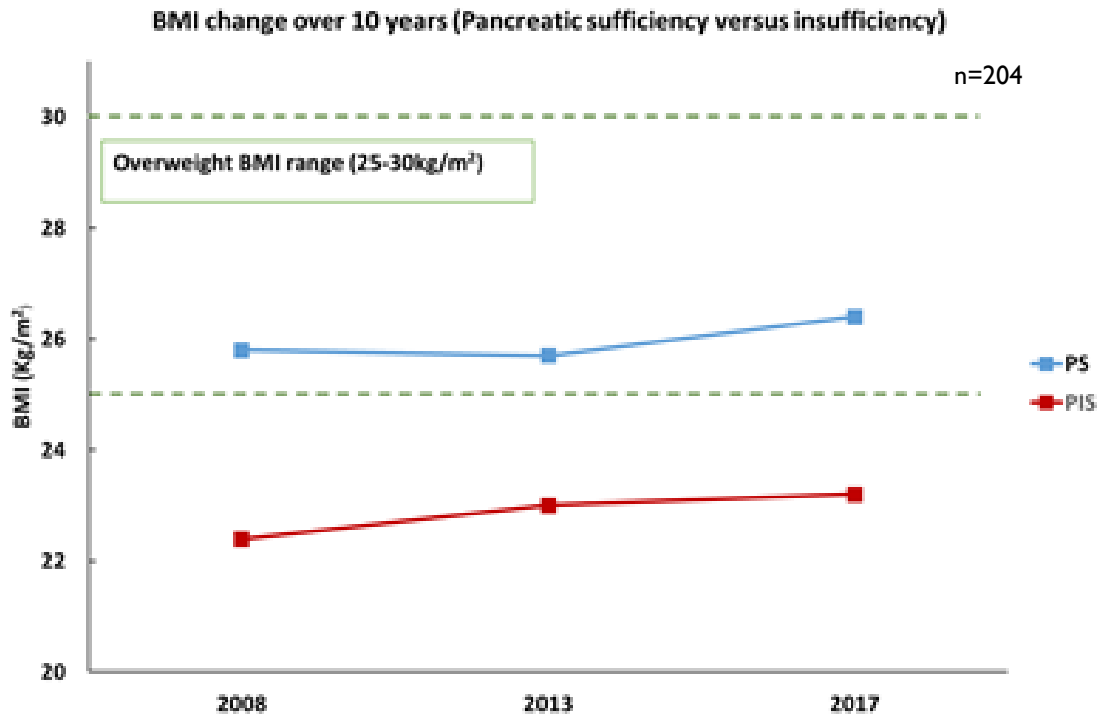


Lesser gains above BMI 22 (women), 23 (men)

Advantages reduce as BMI reaches 30

Adults

LONGITUDINAL CHANGES IN BMI

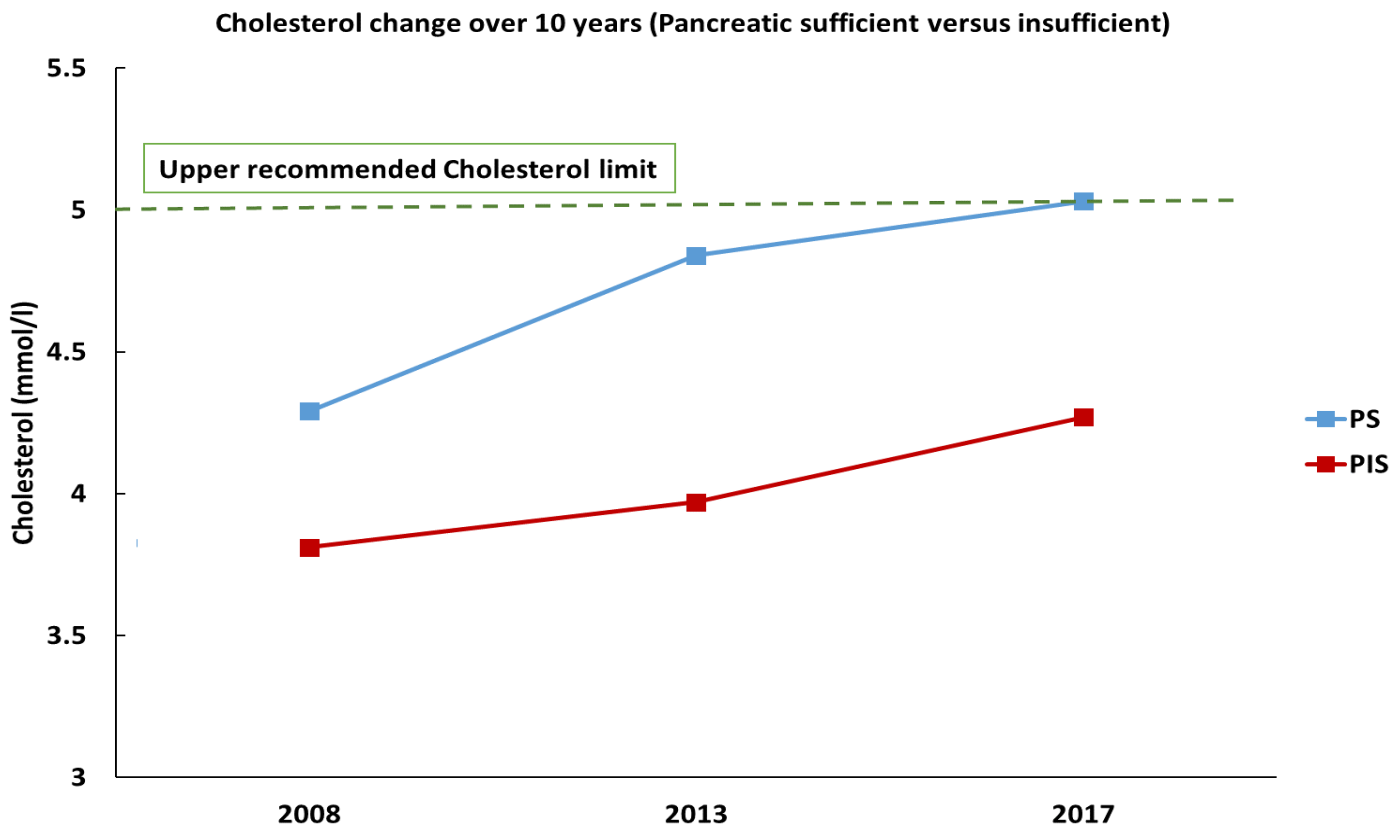


N.J. Greig, H. White, H.K. Chadwick, A. Cartwright, D.G. Peckham
Cardiovascular risk in an adult CF population : a 9 year retrospective analysis

ENERGY & MACRONUTRIENT TARGETS
DIETARY EMPHASIS ON FATS

Fat 35-40% of intake

DIFFERING ADULT POPULATIONS



N.J. Greig, H. White, H.K. Chadwick, A. Cartwright, D.G. Peckham
Cardiovascular risk in an adult CF population : a 9 year retrospective analysis

WHAT TYPES OF FAT?

- Greater longevity
- Vascular endothelial dysfunction shown in children with CF (2013)
- Ischaemic heart disease reported in CF(2010)


SUPPLEMENT

Ischaemic heart disease – a new issue in cystic fibrosis?

Save as

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Introduction

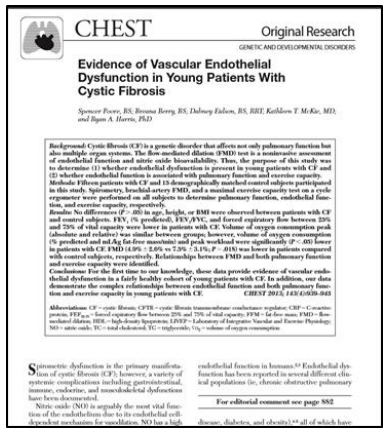
As survival in patients with cystic fibrosis (CF) improves it is likely that new conditions will arise in the aging CF population. There has been speculation that the high-fat diet, which patients are encouraged to eat, and the increasing incidence of CF-related diabetes (CFRD) may put patients at risk of ischemic heart disease (IHD),[1] but to date this has not been seen.

The current case is that of a 48-year-old man, with CF, pancreatic insufficiency and CFRD, who presented acutely with a symptomatic non-ST elevation myocardial infarction (NSTEMI).

Case report

A 48-year-old Caucasian man presented to his local hospital with throat and left arm discomfort. CF was diagnosed when he was 3 months old due to failure to thrive and malabsorption. He had a positive sweat test and was homozygous ΔF508. He was transferred to our Adult Unit aged 16 years, with pancreatic insufficiency on enzyme and vitamin supplements. He has pseudomonas colonization and is on long-term nebulized colomycin, he very rarely requires intravenous antibiotics. He previously worked as a plant manager in a concrete factory and now is self-employed undertaking car body repairs. He has had a long history of depression, requiring prolonged periods of time off work, and has been on long-term antidepressant therapy. Three years prior to the presentation he developed symptomatic hypoglycaemia. An oral glucose tolerance test was suggestive of diabetes (basal sample 4.9 mmol/l, 1normal <7 mmol/l) <7.8 mmol/L]) with HbA$_1$C 6.0% (normal 4.3–6.1%). He did home glucose monitoring and as his levels after meals were not above 9.0 mmol/L, treatment was not initiated. Over the preceding 10 years his weight had increased from 68 kg to 76 kg. At his annual review a few months prior to this presentation he had a BMI of 25.6 kg/m^2 (weight 75.1 kg), FEV$_1$/FVC 3.11 L/min (95%)/4.32 L/min (105%). He did not desaturate with exertion.

He presented with three episodes of throat pain over the preceding 4 days. On the day of admission the pain lasted several hours and radiated to his jaw and left arm. The discomfort was associated with sweating, dizziness and vomiting. He was a non-smoker. There was a family history of cardiovascular disease – his father had had a CVA and a cousin had had a myocardial infarction at the age of 30 years. On examination he was normotensive (108/56), had oxygen saturations of 91% and no evidence of heart failure. ECG showed sinus rhythm with new T wave inversion in leads III and aVF (Figure 1). A random troponin level was raised at 0.11 ug/L (normal <0.05 ug/L) and 12-hour level was 0.54 ug/L. He had normal renal function, random glucose 5.9 mmol/L, C-reactive protein (CRP) <2 mg/L (normal <8 mg/L), total cholesterol 4.2 mmol/l. (normal ≤5.0 mmol/L) and HDL cholesterol 0.91 mmol/L (normal ≥1.0 mmol/L). He underwent coronary angiography and left ventriculogram, as per protocol following presentation with an NSTEMI. There was complete occlusion of the proximal right coronary artery (Figure 2a). He underwent percutaneous coronary intervention (PCI), re-canalization and stent insertion with good effect (Figure 2b).


CHEST Original Research

GENETIC AND DEVELOPMENTAL DISORDERS

Evidence of Vascular Endothelial Dysfunction in Young Patients With Cystic Fibrosis

Spencer Poore, BS; Breana Berry, BS; Dabney Eidson, BS, RRT; Kathleen T. McKie, MD; and Ilgun A. Harris, PhD

Background: Cystic fibrosis (CF) is a genetic disorder that affects not only pulmonary function but also multiple organ systems. The flow-mediated dilation (FMD) test is a noninvasive assessment of endothelial function and nitric oxide bioavailability. Thus, the purpose of this study was to determine (1) whether endothelial dysfunction is present in young patients with CF and (2) whether endothelial function is associated with pulmonary function and exercise capacity.

Methods: Fifteen patients with CF and 15 demographically matched control subjects participated in this study. Spirometry, brachial-artery FMD, and a maximal exercise capacity test on a cycle ergometer were performed on all subjects to determine pulmonary function, endothelial function, and exercise capacity, respectively.

Results: No differences ($P > .80$) in age, height, or BMI were observed between patients with CF and control subjects. FEV$_1$ (% predicted), FEV$_1$/FVC, and forced expiratory flow between 25% and 75% of vital capacity were lower in patients with CF. Volume of oxygen consumption peak (absolute and relative) was similar between groups; however, volume of oxygen consumption (% predicted and mL/kg fat-free mass/min) and peak workload were significantly ($P < .05$) lower in patients with CF. FMD (4.9% ± 2.6% vs 7.3% ± 3.1%; $P = .018$) was lower in patients compared with control subjects, respectively. Relationships between FMD and both pulmonary function and exercise capacity were identified.

Conclusions: For the first time to our knowledge, these data provide evidence of vascular endothelial dysfunction in a fairly healthy cohort of young patients with CF. In addition, our data demonstrate the complex relationships between endothelial function and both pulmonary function and exercise capacity in young patients with CF.

CHEST 2013; 143(4):939–943

Abbreviations: CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; CRP = C-reactive protein; FEV$_{25-75}$ = forced expiratory flow between 25% and 75% of vital capacity; FFM = fat-free mass; FMD = flow-mediated dilation; HDL = high-density lipoprotein; LIVEP = Laboratory of Integrative Vascular and Exercise Physiology; NO = nitric oxide; TC = total cholesterol; TG = triglyceride; $\dot{V}_E$ = volume of oxygen consumption

Spirometric dysfunction is the primary manifestation of cystic fibrosis (CF); however, a variety of systemic complications including gastrointestinal, immune, endocrine, and musculoskeletal dysfunctions have been documented.

Nitric oxide (NO) is arguably the most vital function of the endothelium due to its endothelial cell-dependent mechanism for vasodilation. NO has a high

endothelial function in humans.[13] Endothelial dysfunction has been reported in several different clinical populations (ie, chronic obstructive pulmonary

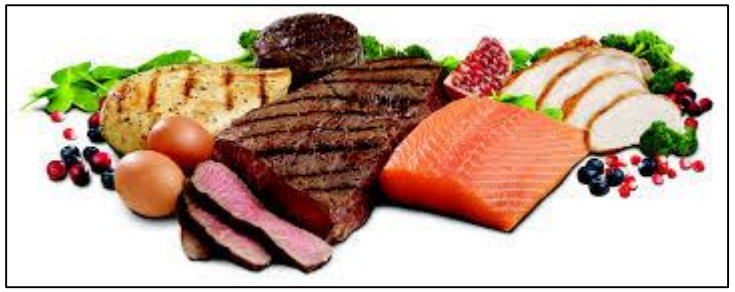
For editorial comment see page 882

disease, diabetes, and obesity),[14] all of which have

- Greater emphasis on polyunsaturated and mono-unsaturated fats
- May also improve essential fatty acid status

- CF Trust (2016) &
- ESPEN-ESPGHAN-ECFS guidelines (2016)

HIGH PROTEIN….?



Protein

No evidence based recommendations for daily protein intake for CF (CF Trust 2016)

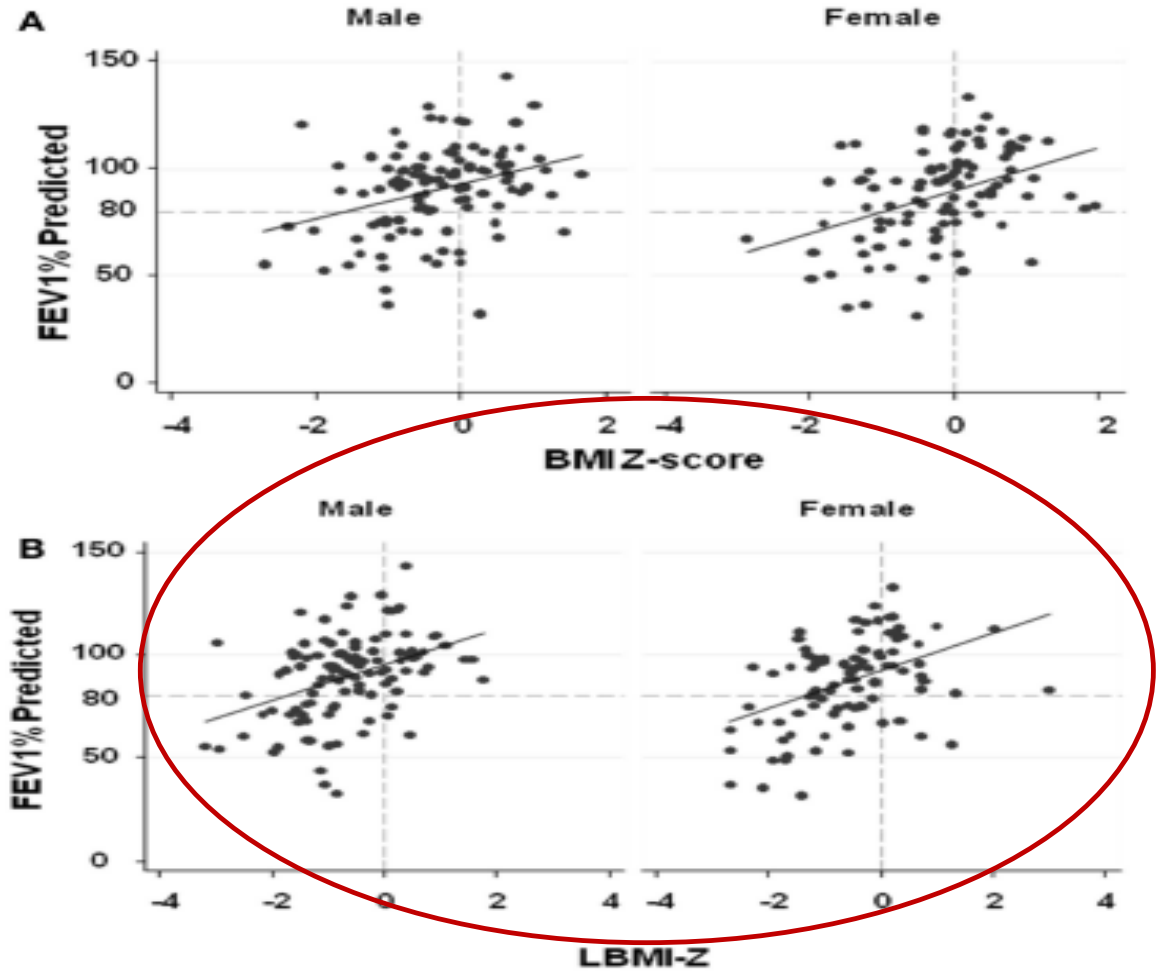
20% energy ESPEN-ESPGHAN-ECFS (2016)

0.83g protein/kg

- Low muscle mass is consistently associated with pulmonary decline
- Protein digestion capacity is severely impaired in CF

SHEIKH ET AL, 2014

- High likelihood of normal lung function, targeting BMI z-score > 0
- Improved further, by targeting LBM z-score >0



SUPPLEMENTS – WHICH ONES?

Complete supplement – small volume (125ml)

Complete supplement – 200ml volume

Fat free supplement – no enzymes required

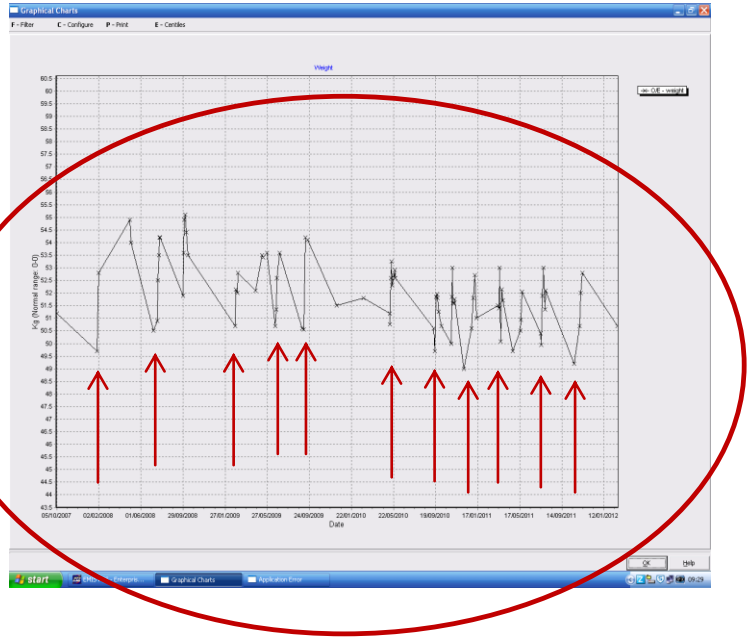
High calorie, high fat supplement (600kcal/240ml drink)

ORAL CALORIE SUPPLEMENTS – COCHRANE REVIEW (2014)


Research

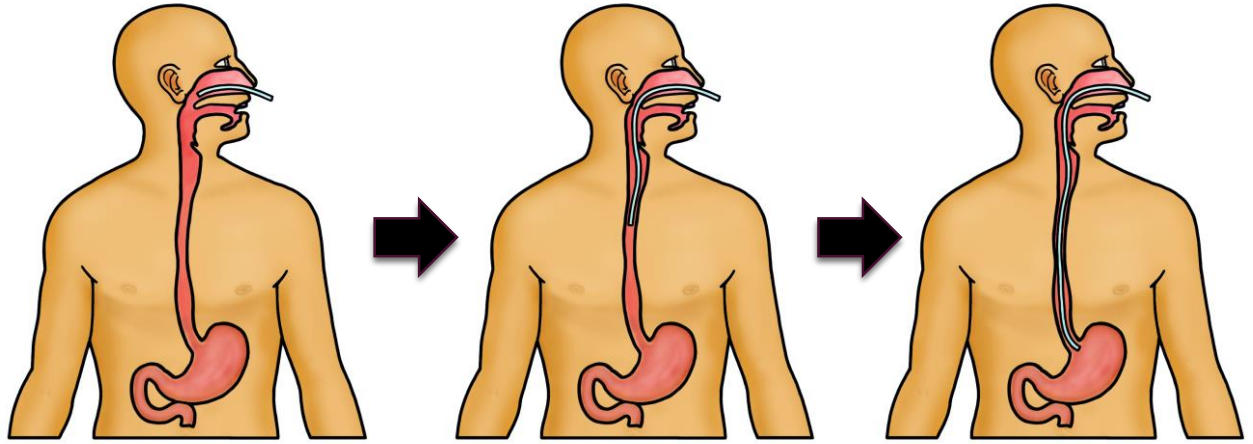
Oral protein energy supplements for children with cystic fibrosis: CALICO multicentre randomised controlled trial

- **Limited trials**
  - **Kalnins et al (2005)**
    - 21 %, 28% intake from oral calorie supplements at 1 and 3 months (mean 1.6 cans/day)
    - No change in weight or height z-score
  - **Hanning et al (2005**)
    - 25 % of EAR energy intake from supplements additional to normal diet
    - No change in weight or height z-score at 6 months
  - **Poustie et al (2006)** Oral protein energy supplements for children with cystic fibrosis: CALICO multicentre randomised controlled trial
    - No improvements in children with cystic fibrosis who were moderately malnourished

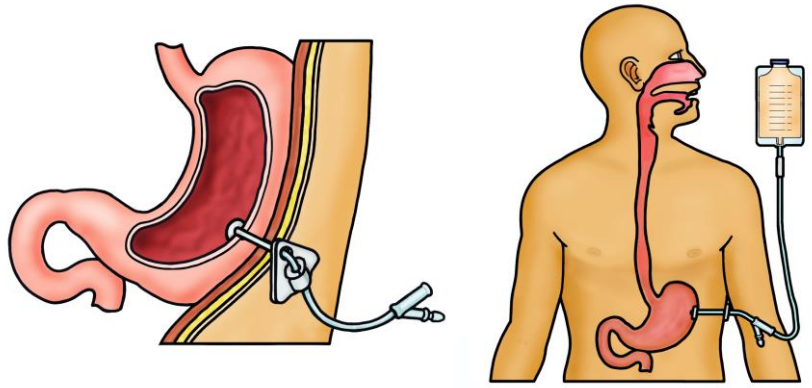


ENTERAL TUBE FEEDING FOR INDIVIDUALS WITH CF: CF FOUNDATION EVIDENCE INFORMED GUIDELINES (2016)

- ETF can improve age dependent anthropometrics
- ETF is given as a continuous overnight infusion



- Cannot recommend ETF to improve or stabilise lung function
- Recommends against FEV_1 being used as a contraindication to PEG or G-Tube placement



ENTERAL TUBE FEEDING - WHAT ARE THE LATEST KEY DOCUMENTS?


Clinical Nutrition xxx (2016) 1–21

Contents lists available at ScienceDirect

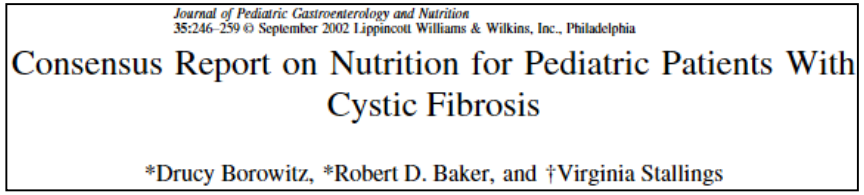
Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

e-SPEN guideline

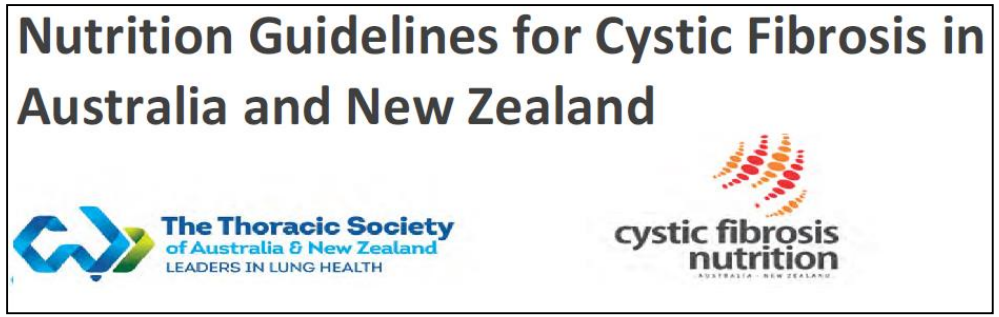
ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis

Dominique Turck [a], Christian P. Braegger [b], Carla Colombo [c], Dimitri Declercq [d], Alison Morton [e], Ruzha Pancheva [f], Eddy Robberecht [g], Martin Stern [h], Birgitta Strandvik [i], Sue Wolfe [j], Stephane M. Schneider [k, l], Michael Wilschanski [l, *, 1]


Journal of Pediatric Gastroenterology and Nutrition
35:246–259 © September 2002 Lippincott Williams & Wilkins, Inc., Philadelphia

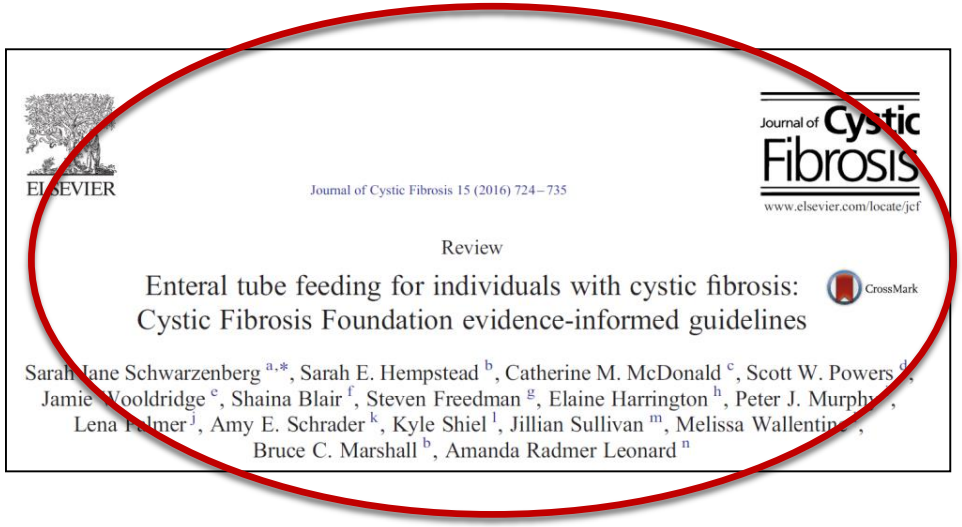
Consensus Report on Nutrition for Pediatric Patients With Cystic Fibrosis

*Drucy Borowitz, *Robert D. Baker, and †Virginia Stallings


Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand

The Thoracic Society of Australia & New Zealand
LEADERS IN LUNG HEALTH

cystic fibrosis nutrition
AUSTRALIA · NEW ZEALAND


ELSEVIER

Journal of Cystic Fibrosis 15 (2016) 724–735

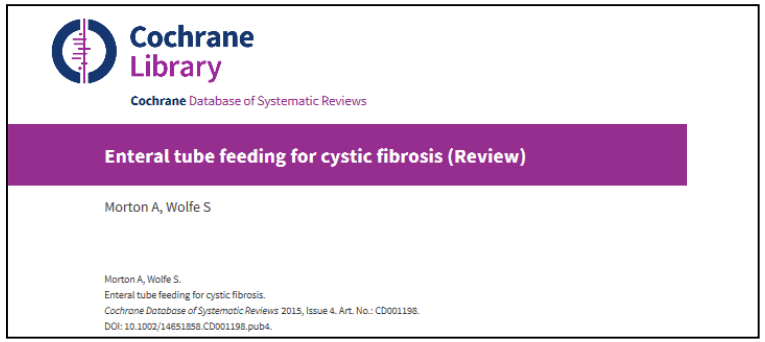
Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Review

Enteral tube feeding for individuals with cystic fibrosis: Cystic Fibrosis Foundation evidence-informed guidelines

CrossMark

Sarah Jane Schwarzenberg [a,*], Sarah E. Hempstead [b], Catherine M. McDonald [c], Scott W. Powers [d], Jamie Wooldridge [e], Shaina Blair [f], Steven Freedman [g], Elaine Harrington [h], Peter J. Murphy [i], Lena Palmer [j], Amy E. Schrader [k], Kyle Shiel [l], Jillian Sullivan [m], Melissa Wallentine [n], Bruce C. Marshall [b], Amanda Radmer Leonard [n]


Cochrane Library

Cochrane Database of Systematic Reviews

Enteral tube feeding for cystic fibrosis (Review)

Morton A, Wolfe S

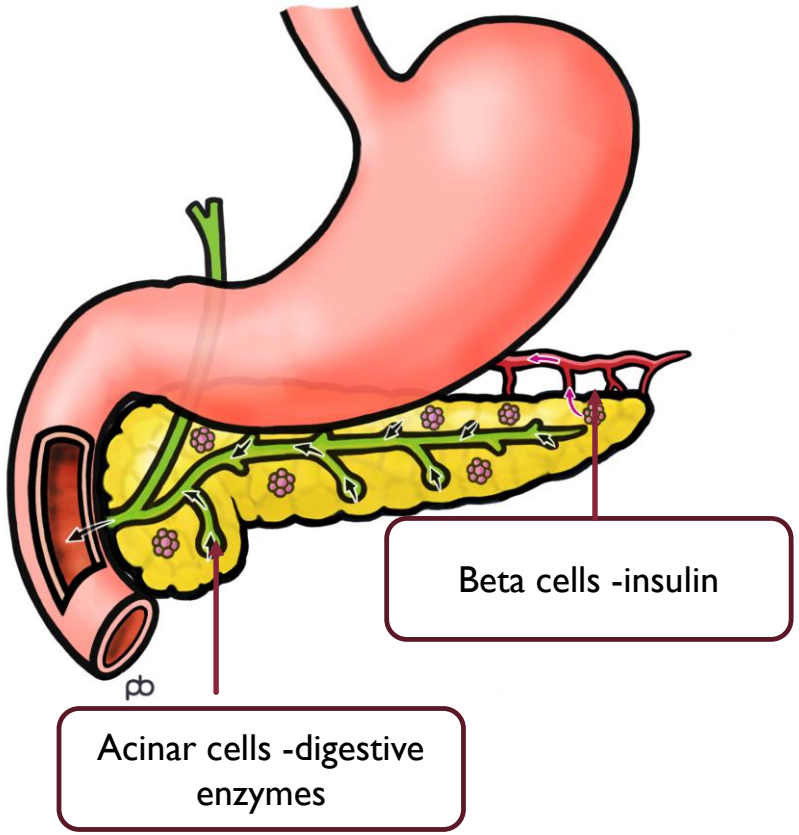
Morton A, Wolfe S.
Enteral tube feeding for cystic fibrosis.
Cochrane Database of Systematic Reviews 2015, Issue 4. Art. No.: CD001198.
DOI: 10.1002/14651858.CD001198.pub4.

WHAT ELSE TO CONSIDER IN OPTIMISING NUTRITION

- High energy/high protein diet
- Oral dietary supplements
- Enteral tube feeding
- Enzyme therapy

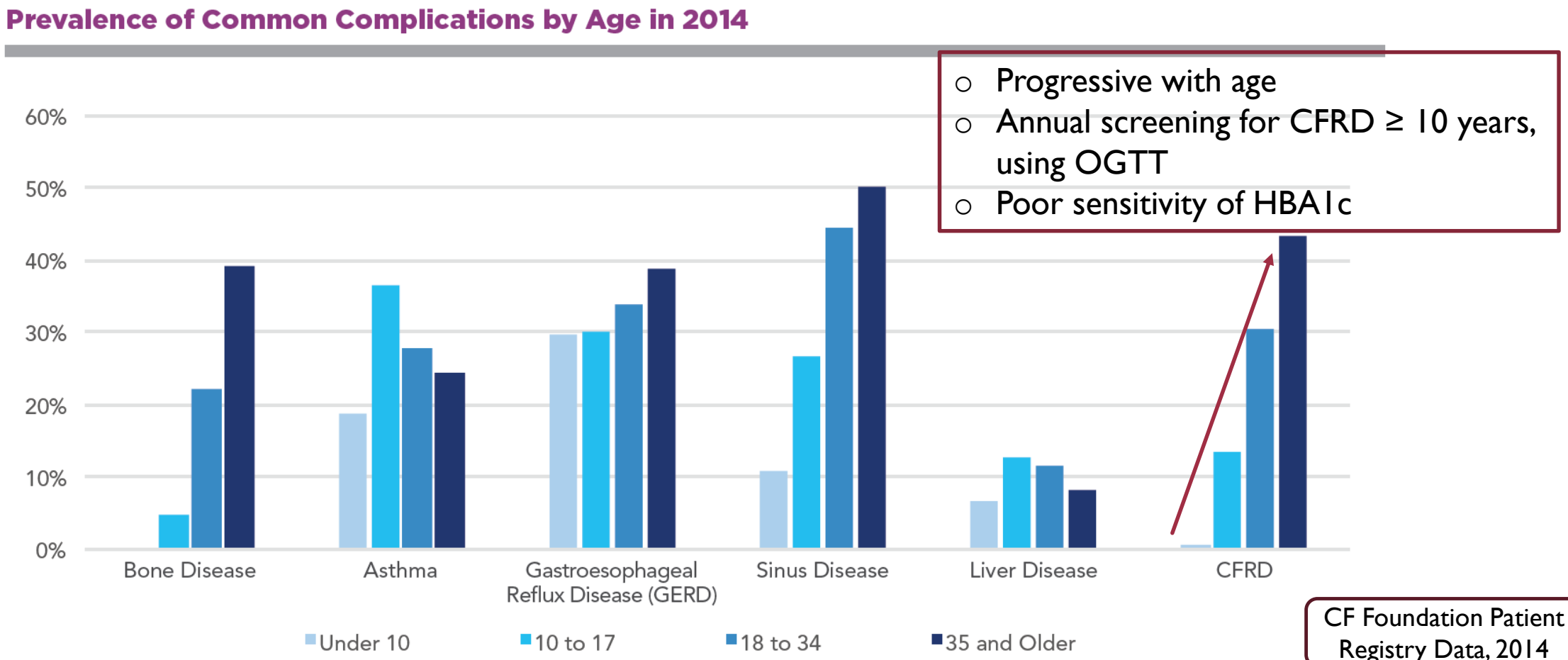
- Vitamin supplementation (A,D,E,K)
- Co-morbidities – cystic fibrosis related diabetes, bone disease
- Pregnancy
- Transplantation
- New therapies

CYSTIC FIBROSIS RELATED DIABETES - THE BASIC DEFECT



- Pancreatic ß cell dysfunction, fatty infiltration and fibrosis
- Causes decreased but not absolute insulin deficiency
- Diabetic ketoacidosis is rare
- Develops insidiously
- Patients may be asymptomatic
- Often first presents where insulin resistance is increased
  - Acute pulmonary infection
  - Chronic severe lung disease
  - Glucocorticoid therapy
  - Immunosuppression regimens (post-transplant)

AT WHAT STAGE DOES IT BEGIN TO OCCUR



- Progressive with age
- Annual screening for CFRD ≥ 10 years, using OGTT
- Poor sensitivity of HBA1c

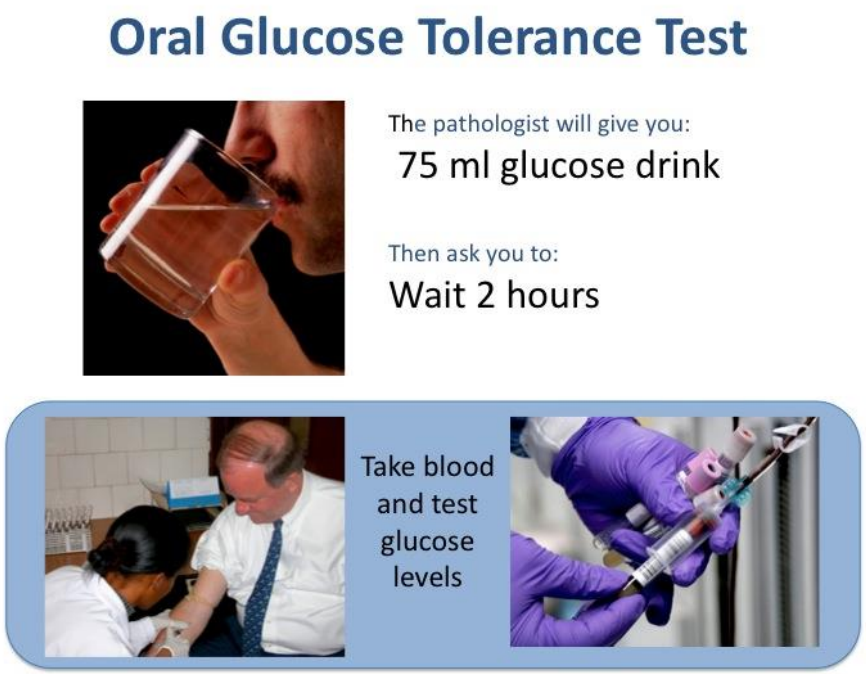
CF Foundation Patient Registry Data, 2014

CYSTIC FIBROSIS RELATED DIABETES CHANGING FOCUS

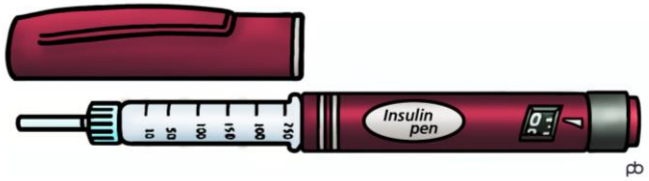
Study	Cohort (n)	Findings for CFRD
Finkelstein et al, 1988	448	Increased mortality Worse nutritional status and lung function
Koch et al, 2001	7756	Worse nutritional status and lung function (greatest discrepancies at puberty)
Sims et al, 2005	2640	Worse pulmonary disease in females
Marshall et al, 2005	8247	Worse nutritional status, increased pulmonary exacerbations, increased liver disease
Adler et al, 2008	8029	Greater risk of CFRD in females Worse pulmonary function and liver function. CFTR class effect
Moran et al, 2009	872	Worse lung function (males) but Gender gap in mortality is narrowing **No nutritional differences** Pulmonary and nutritional differences do not differ by fasting glucose status

CRUCIAL CHANGES TO CARE

- Annual screening using the oral glucose tolerance test

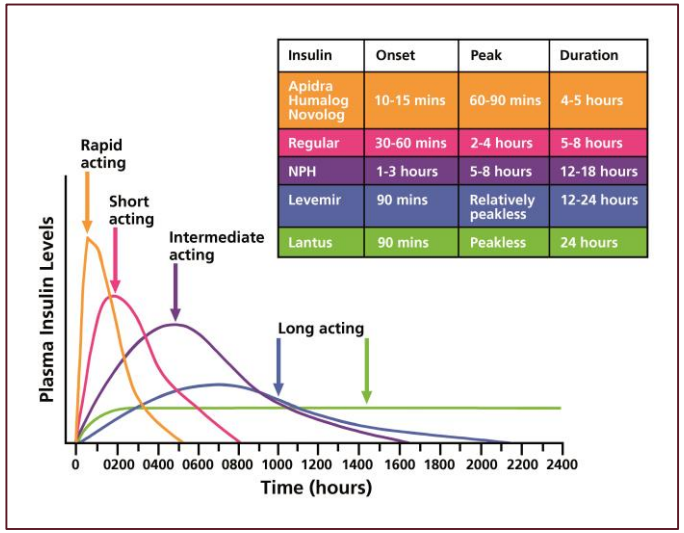


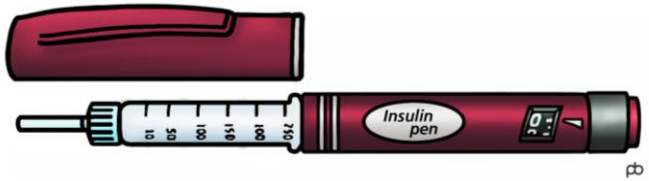
- Early instigation of insulin therapy



NUTRITIONAL GAINS ASSOCIATED WITH INSULIN TREATMENT

	3 months	6 months	1 year	2 year
Moran et al, (2009)			2% ↑BMI	↑
White et al (2009)			3.3% ↑BMI	5.9 % ↑BMI
Nousia Avanitarkis et al, (2001)		16.6% ↑BMI		
Rafii et al, (2005)	2.4% ↑BMI	6.9%↑ BMI		





DIETARY RECOMMENDATIONS … CHANGE?

Update on cystic fibrosis related diabetes Kelly A, Moran A [Journal of Cystic fibrosis 2013:12;318-331]

- Consuming simple CHO in combination with complex CHO, protein and fat may limit the glucose excursion

CF Trust Nutritional management of Cystic Fibrosis (2016)

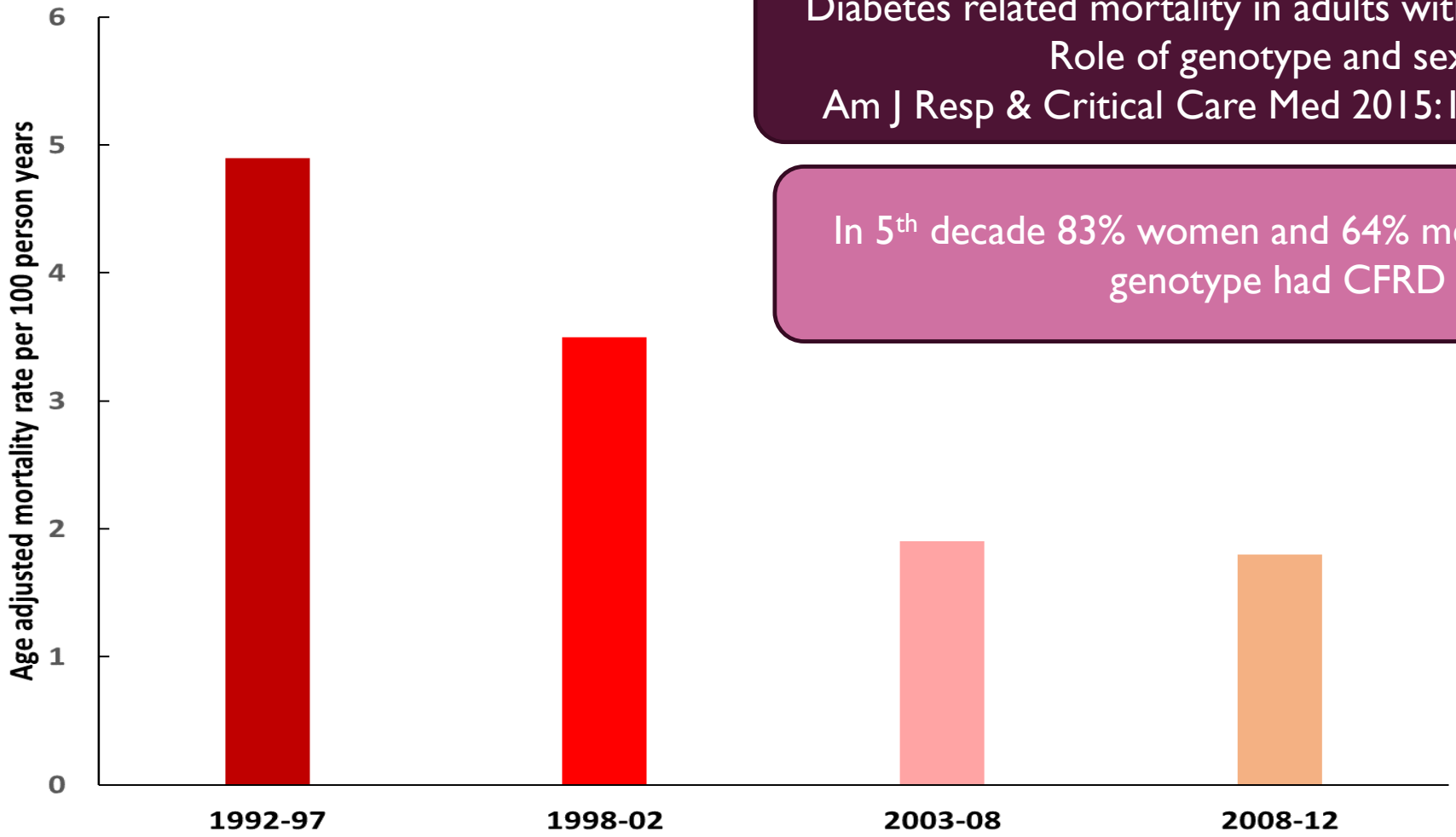
- Type I /II advice inappropriate
- Some people may be taught CHO counting
- If they do not CHO count regular meals should be encouraged containing complex CHO and limiting simple CHO to mealtimes

Insulin initiation and dose adjustments should be done conservatively - to avoid hypoglycemia.

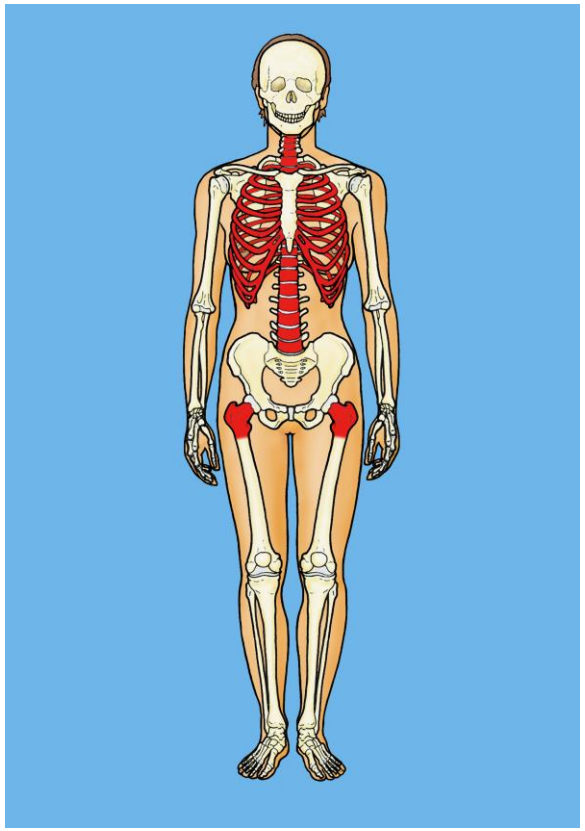
LEWIS ET AL (2015)
DIABETES – RELATED MORTALITY IN ADULTS WITH CYSTIC FIBROSIS

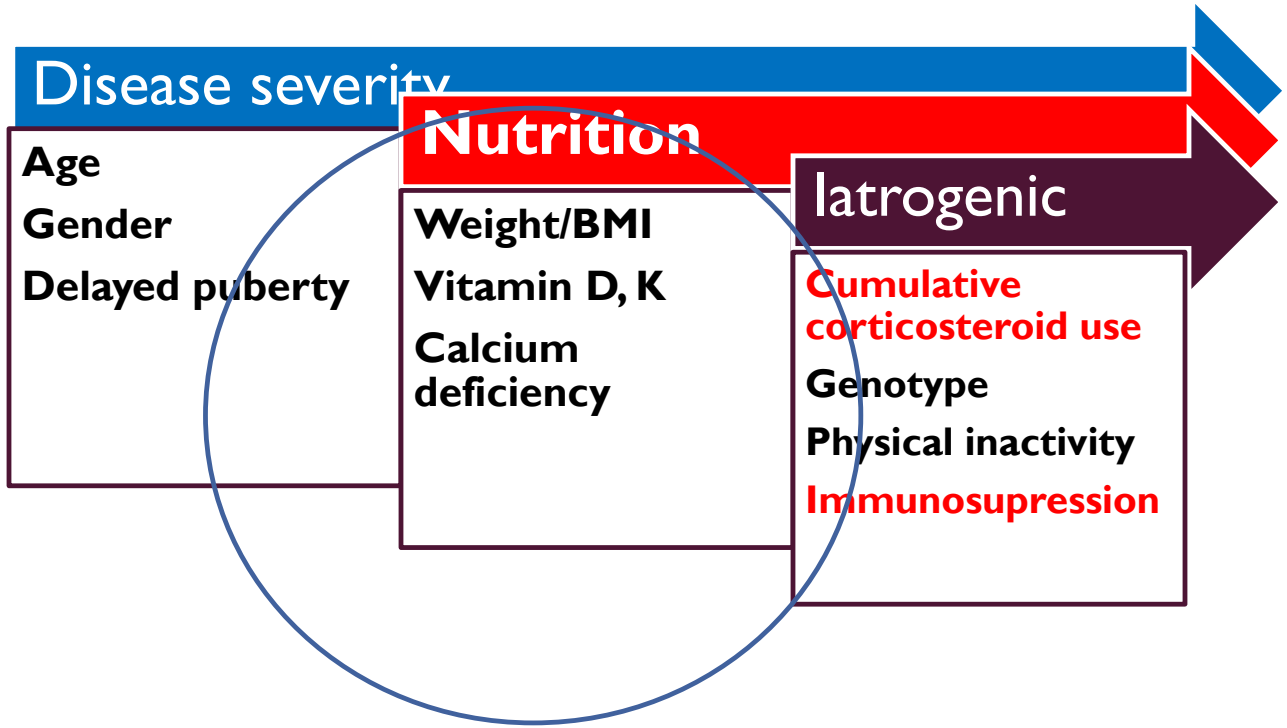
Diabetes related mortality in adults with cystic fibrosis: Role of genotype and sex
Am J Resp & Critical Care Med 2015:191(2);194-200

In 5th decade 83% women and 64% men with a severe genotype had CFRD



TREATMENT CONSIDERATIONS FOR PREVENTING LOW BONE MINERAL DENSITY

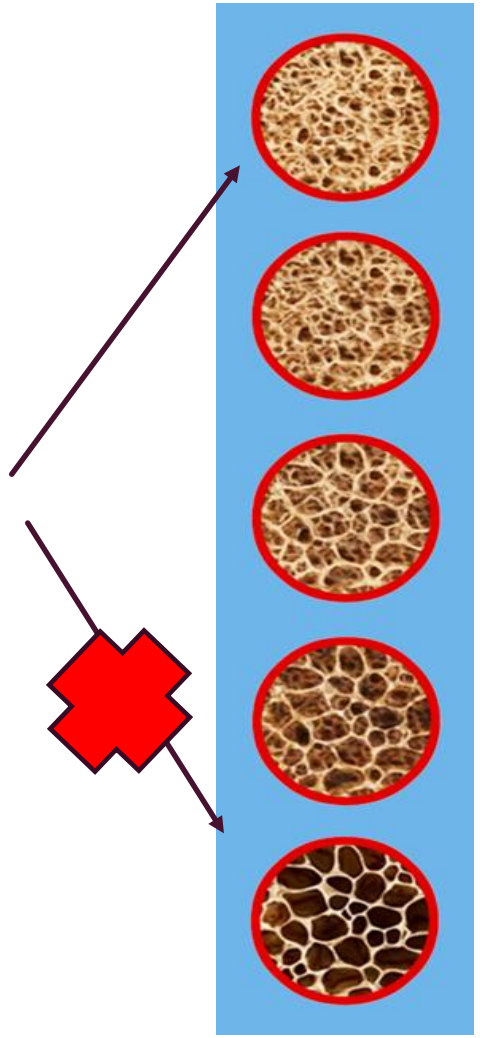




Increased prevalence of bone mineral density

A NUTRITIONAL PROBLEM

Requirements for normal bone mineralisation	
Adequate bone mass	(especially during the growth spurt)
Protein	osteoid formation
Vitamin D	Calcium absorption and phosphate utilisation
Calcium, phosphate and Magnesium	Bone calcification and mineralisation
Vitamin K	Carboxylation of osteocalcin



RISK FACTORS FOR VITAMIN D DEFICIENCY IN CF

- Reduced absorption *Lark et al, 2001*
- Inadequate supplementation
- Non adherence to therapy
- Reduced stores due to depleted fat mass
- Reduced sunlight exposure because of illness and medications
- Low vitamin D binding proteins *Speeckaert et al, 2008*
- Mg deficiency causes functional vitamin D deficiency (renal 25 OHD to 1,25$(OH)_2D$)

VITAMIN D INSUFFICIENCY PERSISTS IN CF

	Paediatric	Insufficiency/deficiency
Canada	Grey et al, 2008	88% insufficient
USA	Green et al 2008	46% insufficient
France	Sermet-Gaudelus et al, 2008	90% insufficient
UK	Conway et al., 2008	78% insufficient 15.0% deficient
Russia	Asherova et al, 2008	41.7% insufficient 16.6% deficient

TRENDS IN BMD STATUS

- Vitamin D intakes had increased by 53%
- Contributing factors may include steroid use, low BMI, inadequate calcium and vitamin D intake, and poor nutrient absorption, as well as effects of gene mutation on bone cells

ELSEVIER

Journal of Cystic Fibrosis 14 (2015) 526–532

Journal of Cystic Fibrosis

Original Article

Trends in bone mineral density in young adults with cystic fibrosis over a 15 year period☆

Melissa S. Putman [a,b,g], Joshua F. Baker [c], Ahmet Uluer [d], Karen Herlyn [e], Allen Lapey [f], Leonard Sicilian [g], Angela Pizzo Tillotson [h], Catherine M. Gordon [h,i], Peter A. Merkel [c], Joel S. Finkelstein [a]

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[b] Division of Endocrinology, Boston Children's Hospital, Boston, MA, United States
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[f] Pulmonary Division, Department of Pediatrics, Massachusetts General Hospital, Boston, MA, United States
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VITAMIN D SUPPLEMENTATION

- > 1 years 1,000-5,000 IU Vitamin D_3/day

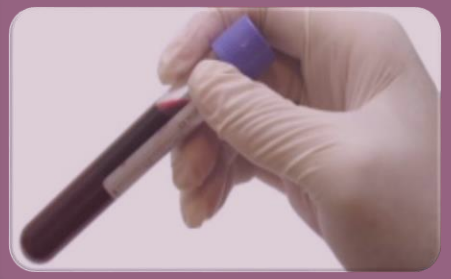
ECFS, 2011

- Aiming for minimum of 50nmol/L

CONTINUED DEBATE

- Target serum level >20 or >30ng/ml (50-75nmol/l) – mixed guidance
- Timing (Possible improved absorption with food and enzymes)
- Vitamin D2 or Vitamin D3? - Vitamin D3 (Cholecalciferol)
- Intervals (no evidence for bolus versus daily dosing)
- UV lamps (no recommendation)

GREATER CERTAINTY…



Vit D measured by total serum 25(OH) D as it is associated with health outcomes, is the primary circulating form of Vit D and accounts for Vit D from diet & sunlight

Assess during the winter months (winter levels shown to be only 70% of summer values)

Repeat intervals following changes in treatment should be undertaken at 3 months

CALCIUM

- Should be assessed at least annually (ESPEN-ESPGHAN-ECFS Guidelines)
- Daily calcium intakes should be at a minimum to achieve dietary intake recommended by the EFSA

Calcium intake for people with CF: recommendations guided by EFSA

Age	Dietary reference values
0-6 months	200mg
7-11 months	280mg
1-3 years	450mg
4-10 years	800mg
11-17 years	1150mg (1300mg 9-18yrs)
18-25 years	1000mg
>25 years	950mg

VITAMIN K

- Sub clinical as assessed by increased PIVKA II- almost universal in CF *Conway et al, 2005; Rashid et al, 1999; Becker et al, 1997; Wilson et al,1997*
- Increased % of undercarboxylated osteocalcin (Glu-Oc) *Fewtrell et al, 2008; Grey et al, 2008; Nicolaidou et al, 2006; Conway et al, 2005; Aris et al, 2003*
- Associated with increased bone turnover
- Reduced markers of bone mineral accrual

ecfs

European Guidelines – routine supplementation of all pancreatic insufficient patients

Infants 0.3-1mg/day

Older children and adults 1-10mg/day

Cystic Fibrosis our focus

CF CYSTIC FIBROSIS TRUST

UK (CF Trust, 2016)
routine supplementation of all pancreatic insufficient patients (phytomenadione)

Babies & infants <2 years 300µg/kg/d

2-7 yrs 5mg/day

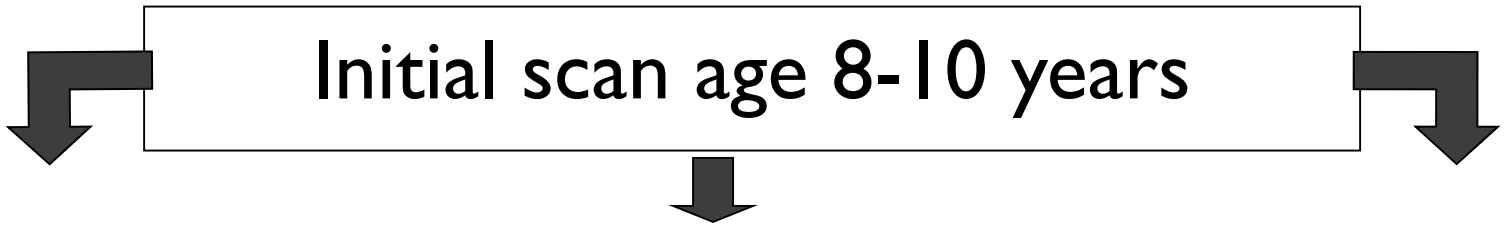
> 7 yrs 5-10mg/day

European Cystic Fibrosis Bone Mineralisation Guidelines

'If height is ≥1 SD below age and sex matched healthy controls, BMD Z scores should be adjusted for height or statural age to avoid overestimating deficits in BMD in people with short stature'

Stress the importance of serial height adjusted measurements
Sermet-Gaudelus et al, 2011

ECFS, 2011



Normal LS Z score

Rescan every 5yrs

LS Z score -1 to -2

Rescan every 2yrs

LS Z score <-2 "CF related low BMD"

Rescan every yr

SUMMARY

- Greater complexity of nutritional management and emergence of new therapies
  - Diet, oral supplementation, enteral tube feeding
  - Pancreatic enzyme therapy introduction
  - Vitamin Supplementation (Vitamin A,D, E, K)
  - Cystic fibrosis related diabetes, osteoporosis, management of pregnancy, post-transplantation…. and others
    - Improvements in nutritional status over the last 10 years aligned with earlier and more aggressive interventions across all aspects of nutritional management
    - …..The future for our adult populations?