Preventative treatment of osteoporosis in children with CF

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Poor bone mineral density in children with CF

1. Why is it a concern?
2. How do we minimise risk factors
3. Which risk factors do we target and what do we aim for?

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Defining CF bone disease and osteoporosis

- The term CF related low bone mineral density' can be applied to children with a BMD z score of below -2

- In CF children and adolescents up to the age of 20 osteoporosis is defined as having a BMI z-score of below -2 and a significant fracture history

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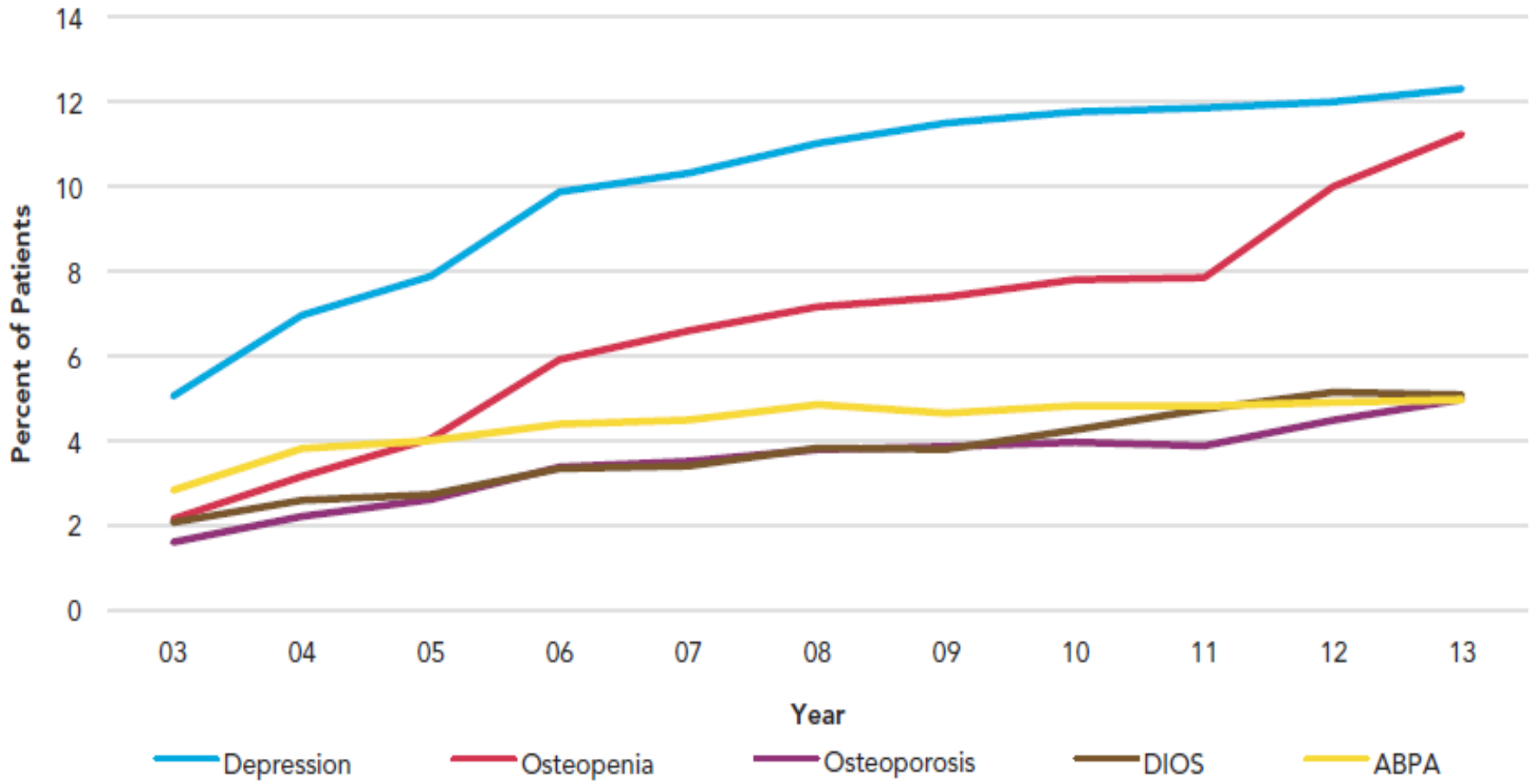
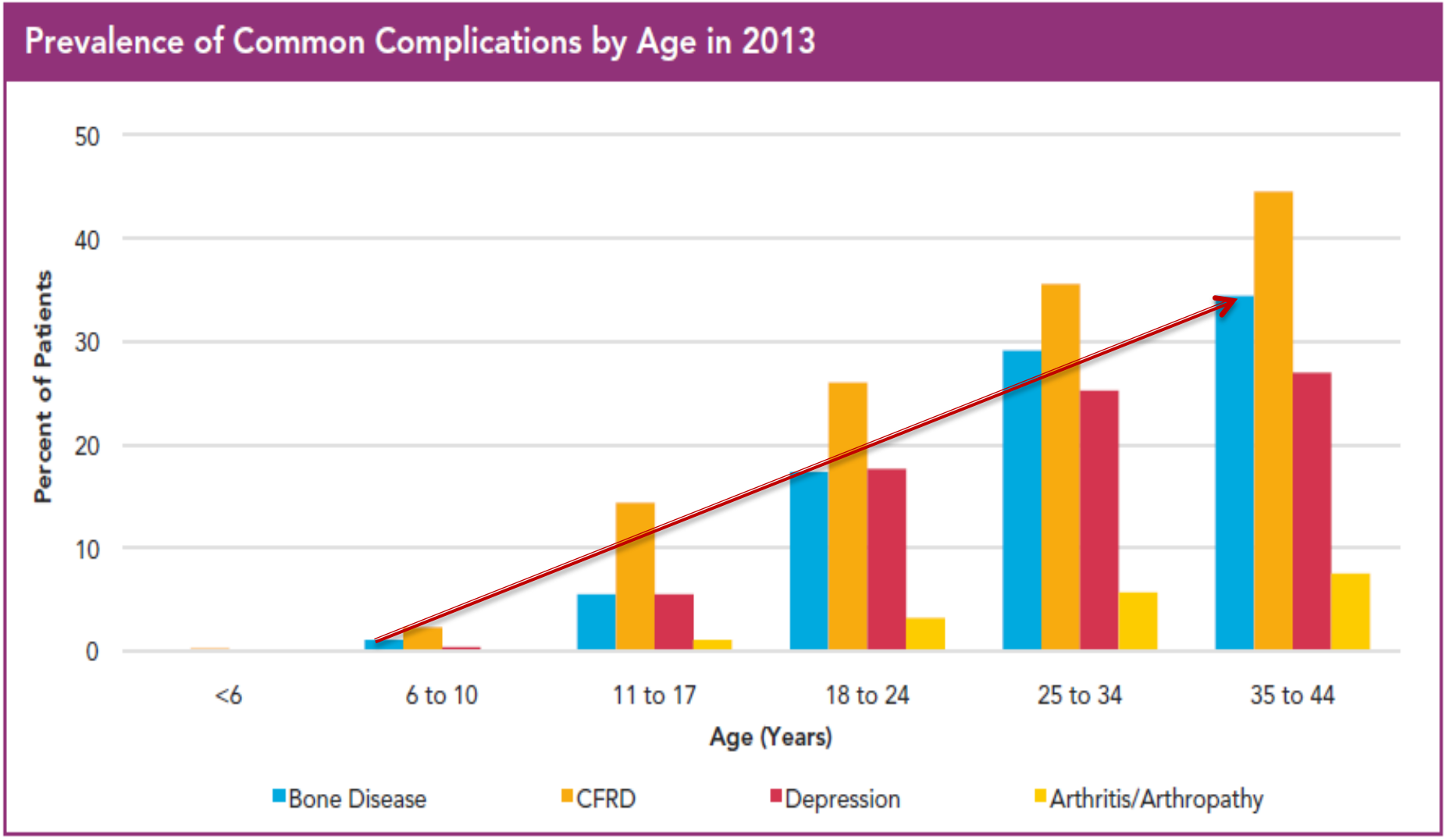
Prevalence

Prevalence of Complications, 2003–2013

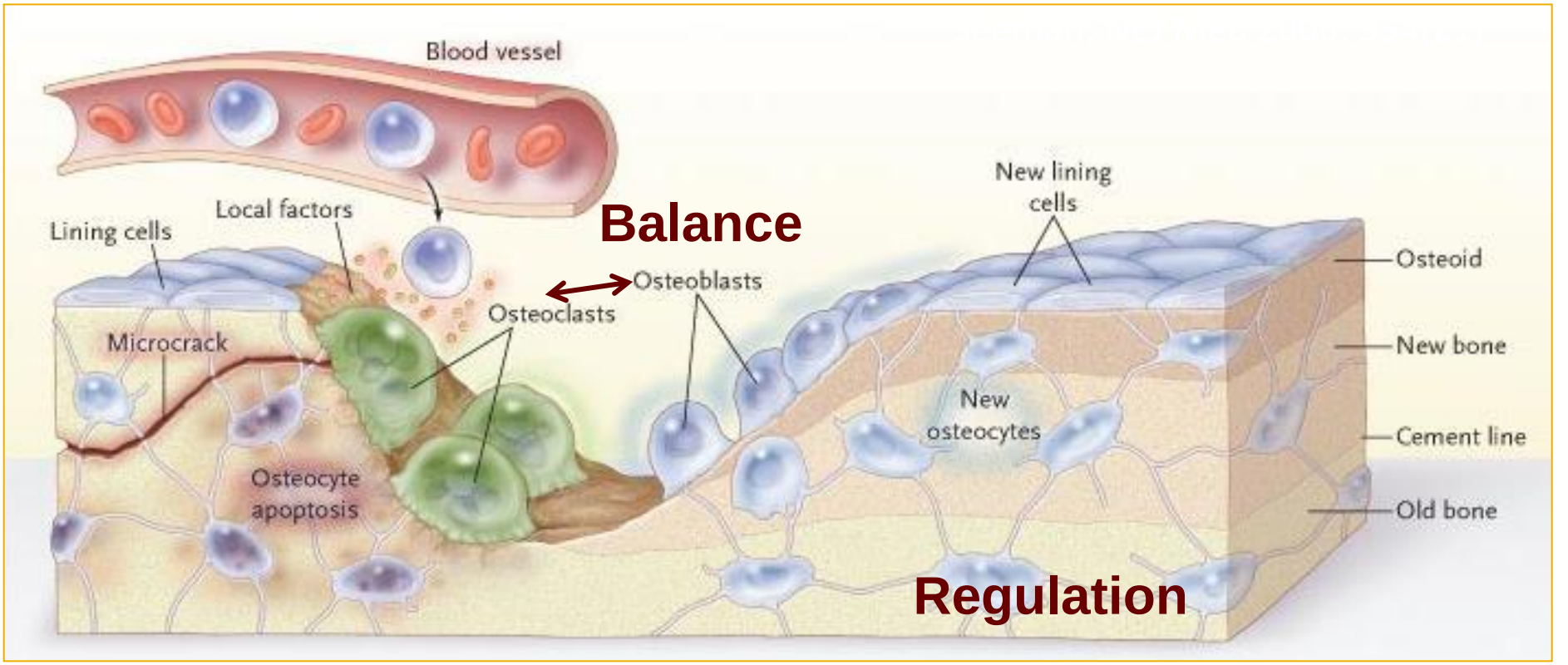


CF Foundation, 2015

At what stage in childhood does it begin to occur



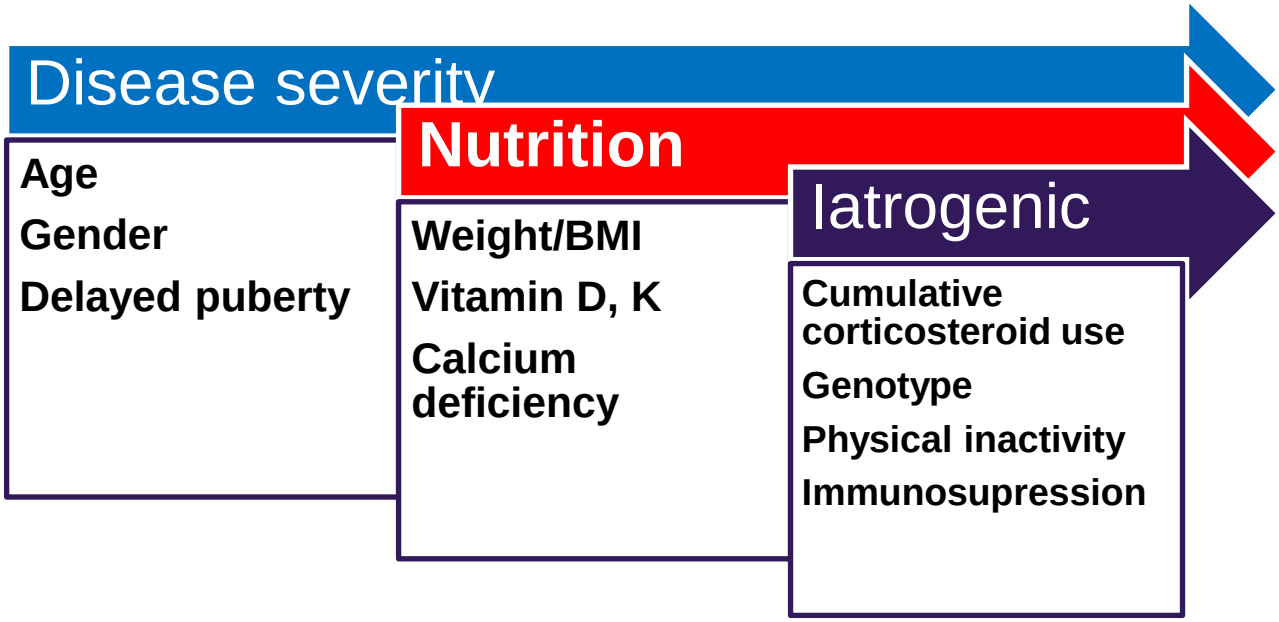
Bone remodeling
- a dynamic process



Resorption **Formation**

From: Hendriks JJE NACFC 2008

Treatment considerations for preventing low bone mineral density



Reduced prevalence of bone mineral density

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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

Nutritional status and BMD

- Strong evidence that nutritional status predicts BMD
- **Haworth et al., 1999 and Conway et al., 2000** BMD significantly correlated with BMI
- **Mischler et al., 1979** all patients with low BMD were < 5th centile for height
- **Fok et al., 2002** BMI percentile position identifies those at risk. Aggressive nutritional treatment should start when BMI < 25th percentile

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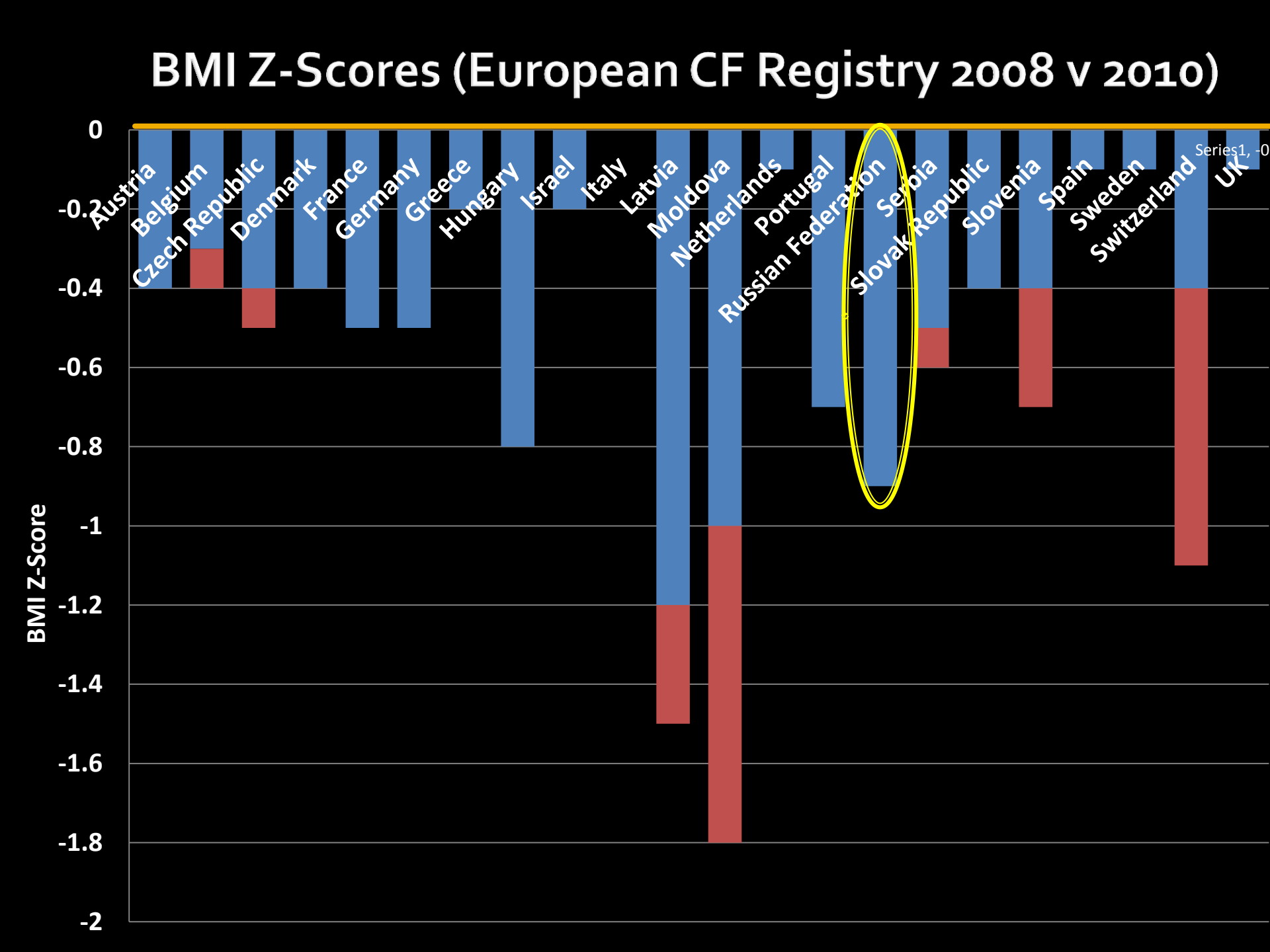
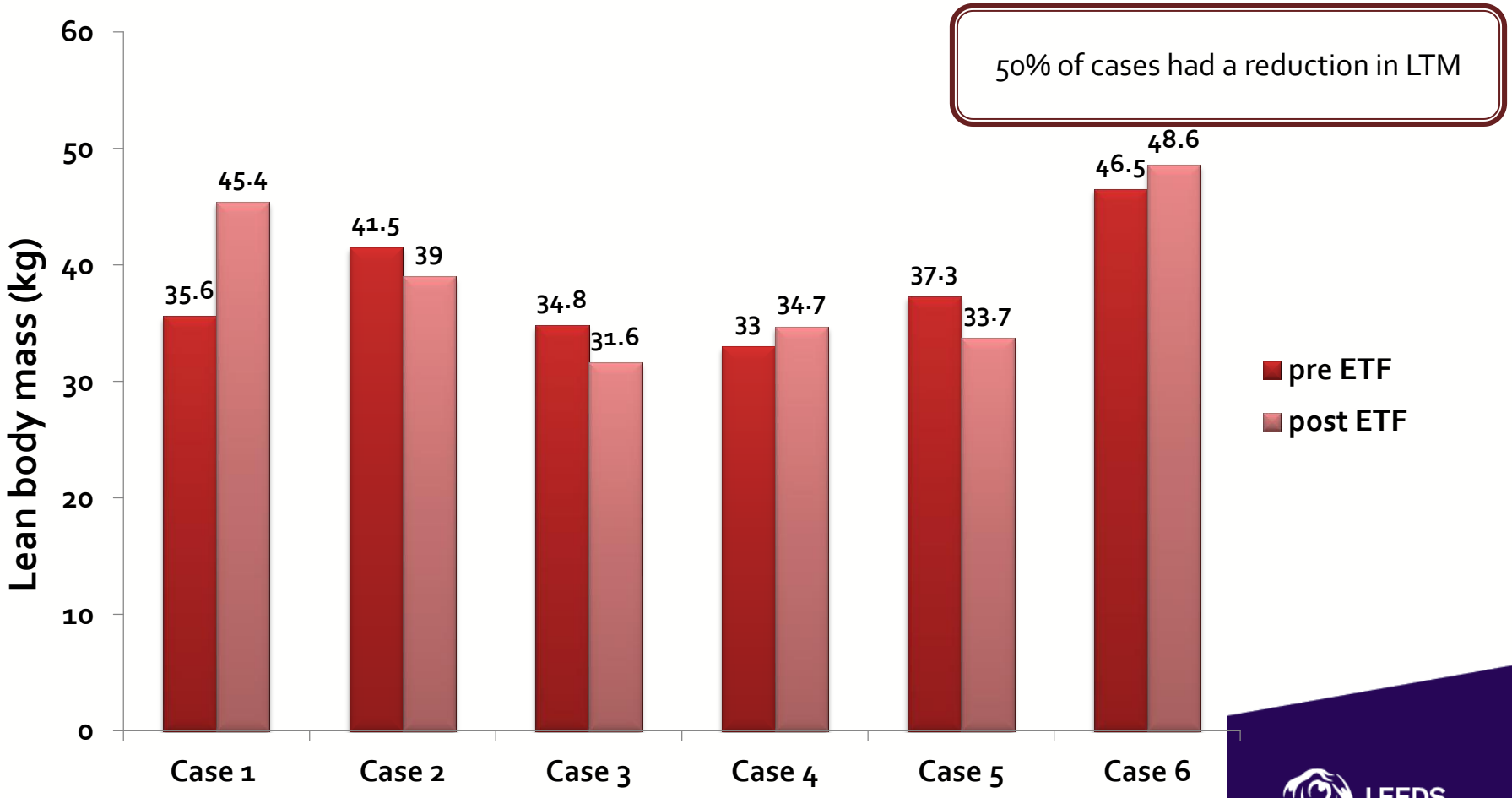

BMI Z-Scores (European CF Registry 2008 v 2010)
BMI Z-Score
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
-1.4
-1.6
-1.8
-2
Austria
Belgium
Czech Republic
Denmark
France
Germany
Greece
Hungary
Israel
Italy
Latvia
Moldova
Netherlands
Portugal
Russian Federation
Serbia
Slovak Republic
Slovenia
Spain
Sweden
Switzerland
UK
Series1, -0

Lean tissue mass and BMD

- Body muscle exerts the largest load and strain on bone and influences size, geometry & density
- LTM is an independent predictor of bone mass in cystic fibrosis *(Sermet Gaudelus et al, 2007)*
- Numerous studies have found correlations between weight, height, % fat, lean tissue mass, fat free mass with a BMD, volumetric BMD and bone mineral content in both adult and paediatric patients

Maximising nutritional status & body muscle mass is important to maximise Bone Mass accrual

Changes in lean tissue mass from pre to post-start enteral tube feeding



White et al., 2014

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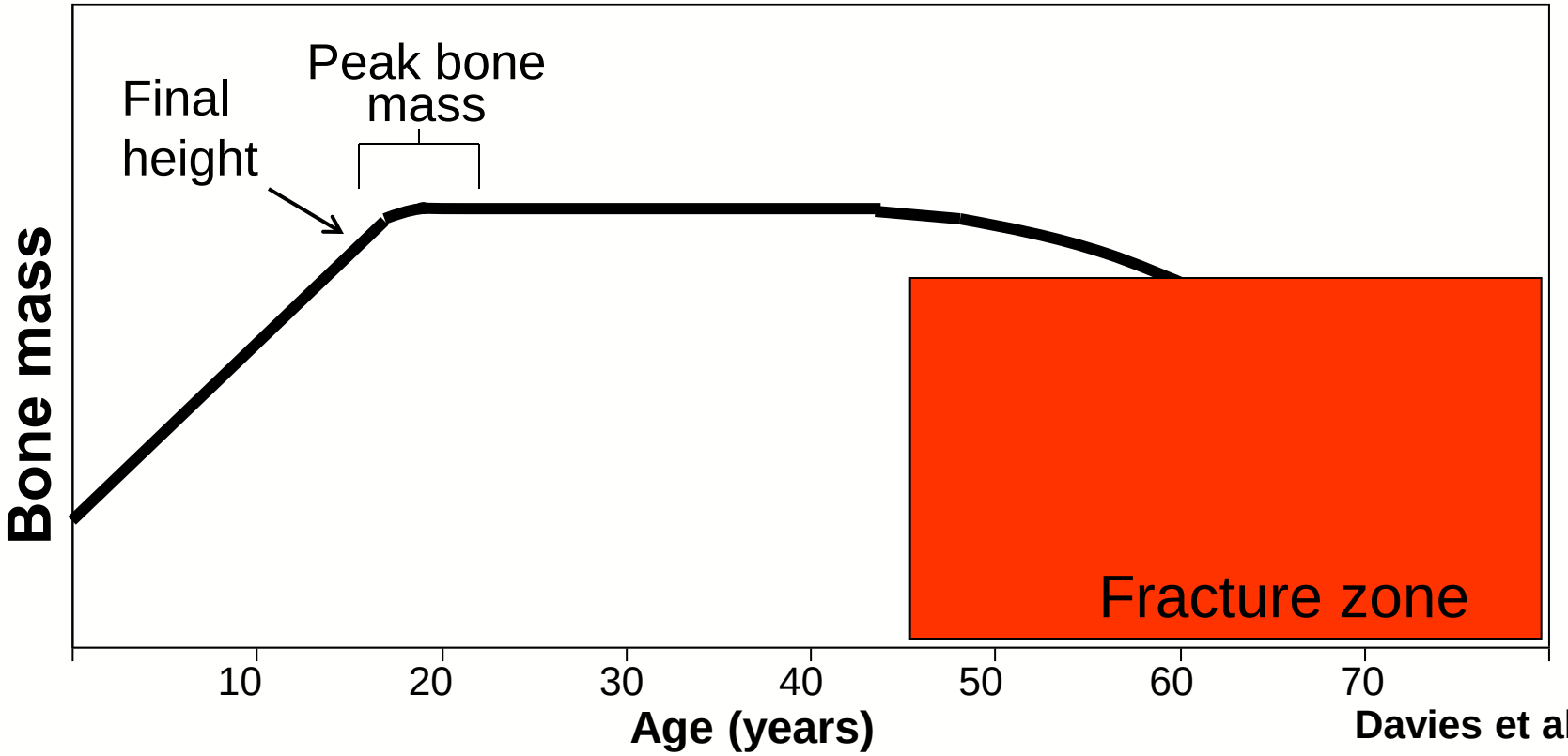
Normal bone mineral accrual



Davies et al, 2005

- 95% peak bone mass achieved by the end of the pubertal growth spurt
- Bone acquisition is more closely correlated with pubertal stage than with chronological age

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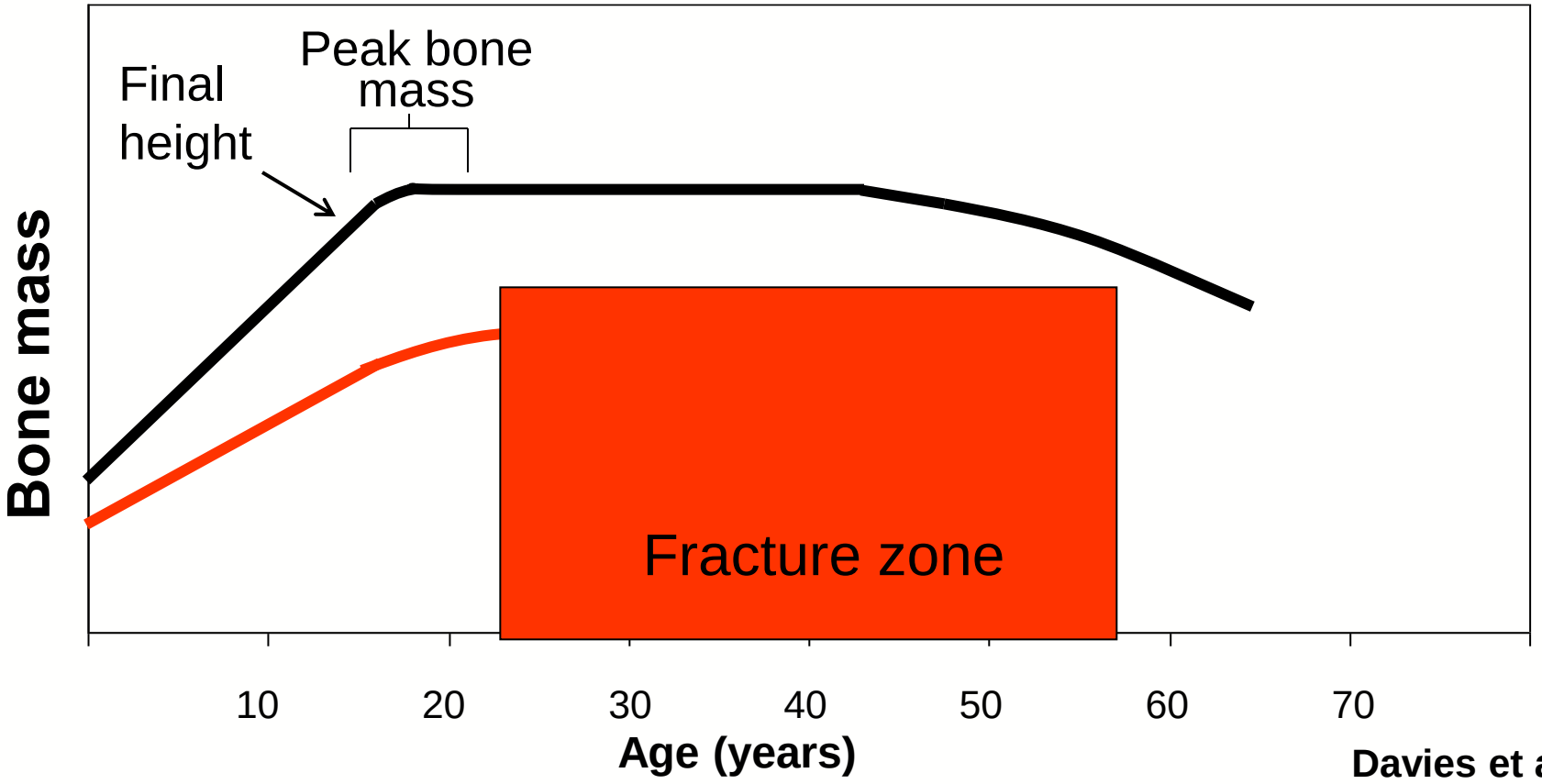
Suboptimal bone mineral accrual



Davies et al, 2005

- Delayed puberty may retard bone growth & development of peak bone mass
- Pubertal delay of only 2 years may be very important

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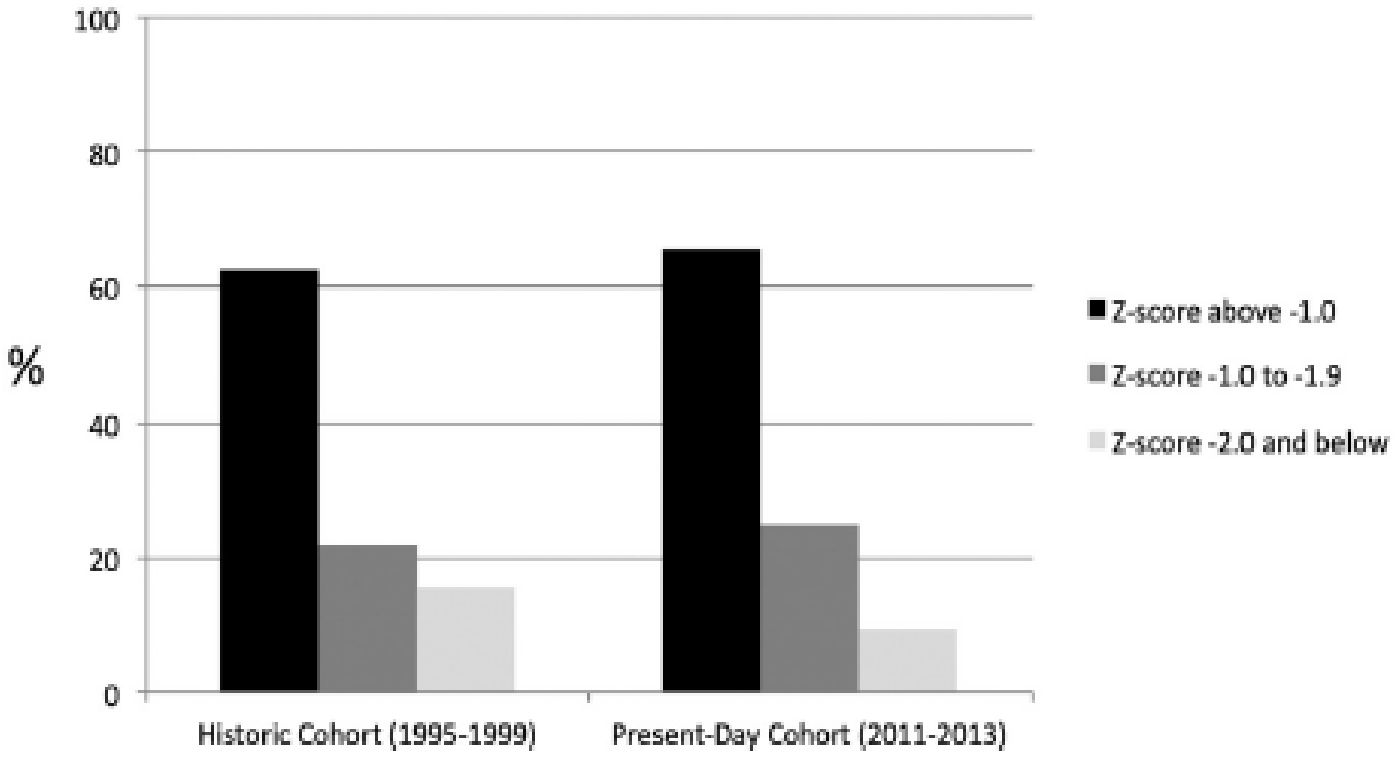
% of patients with normal or reduced BMI z-score (historic v present day cohort)



Putnam et al, 2015 J Cysts Fibros

Continued dietary emphasis……

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High protein….

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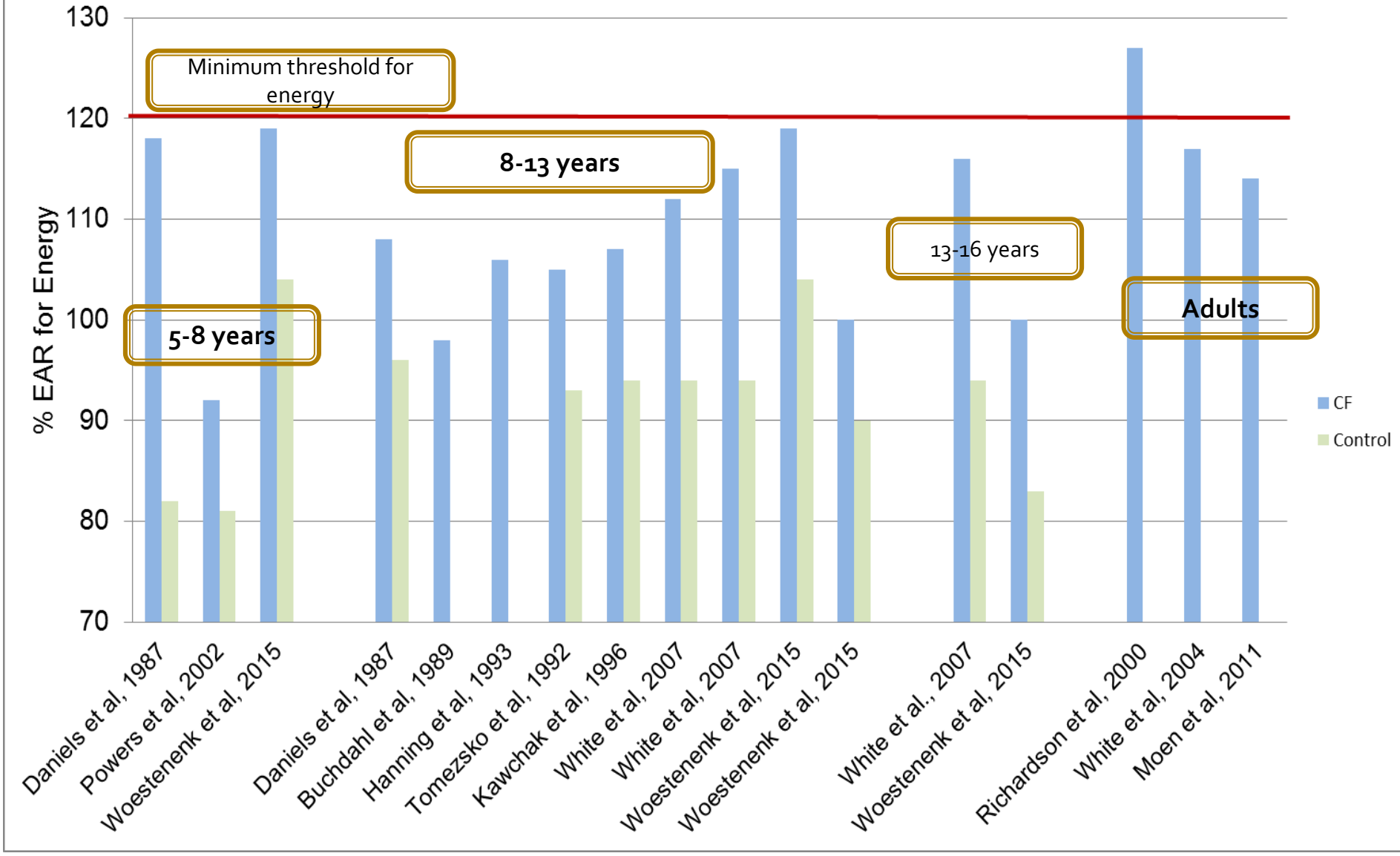
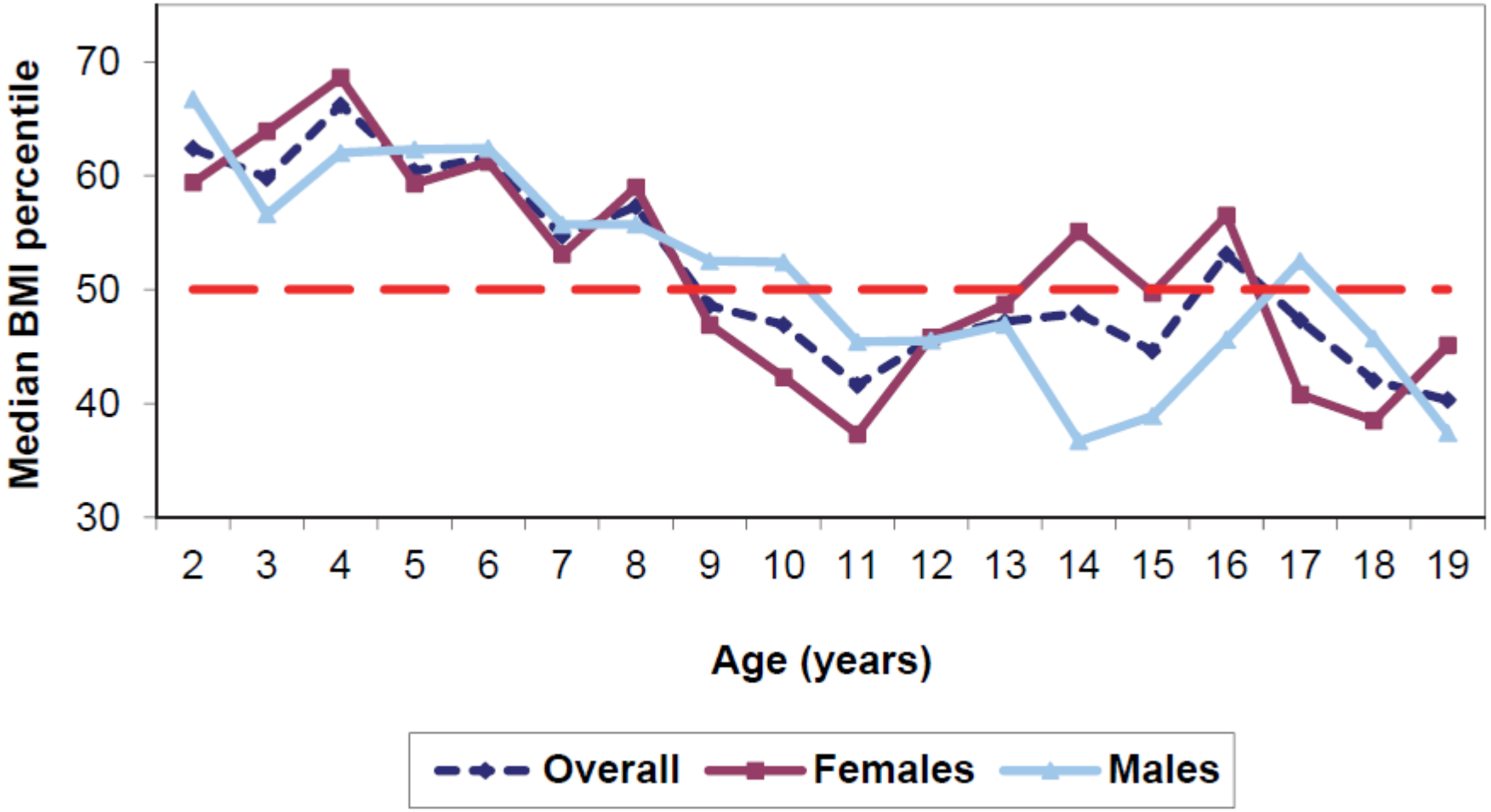
Comparison of studies reporting energy intakes in child, adolescent and adult populations



Median BMI amongst children and young people < 20 years



CF Trust Annual data report, 2013

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*
- ? abnormal 1 α hydroxylase in kidney due to renal CFTR

  Greer et al, 2003
- Mg deficiency causes functional vitamin D deficiency (renal 25 OHD to $1,25(OH)_2D$)

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7-dehydrocholesterol in skin

(SPF ≥ 8, clothes, glass)

(–)

Major Source: Sun

UVB (290-315 nm)

Vitamin D_3 (Cholecalciferol)

Minor Source: Dietary

Vitamin D_2 (ergocalciferol):
Plants/supplements

Vitamin D_3 (Cholecalciferol):
Fish (cod liver oil), meat, fortified milk, egg yolk, butter

Parathyroid hormone

(+)

1-hydroxylase

25-hydroxyvitamin D_3
25(OH) D_3

1,25-dihydroxyvitamin D_3

↑Calcium absorption (small intestine)
↑Urinary calcium reabsorption (kidney)
↑Bone mineralization

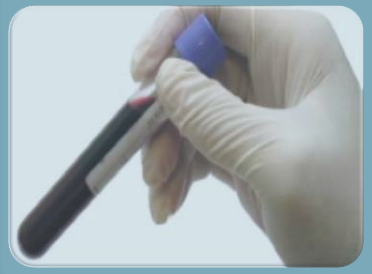
Vitamin D insufficiency persists in CF

	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

Continued debate…

- Target serum level >20 or >30ng/ml (60-75nmol/l) – mixed guidance
- Timing (Possible improved absorption with food and enzymes)
- Vitamin D2 or Vitamin D3? - Vitamin D3 (Cholecalciferolol)
- Intervals (no evidence for bolus versus daily dosing)
- UV lamps (no recommendation)

Greater certainty…



Vit D should be 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)
(Barrett et al, Asherova et al)

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

Vitamin D supplementation

- 0-1 year - 400-500IU Vitamin D_3/day (1ml of vitamin preparations
- <10ng/ml (25nmol/l) urgent management
- >20<30ng/ml (>50nmol/l<75nmol/l) urgent management – and confirmed adherence
- increase to 800-1000IU Vitamin D_3/day by Vitamin D only
- >10 years 800-2000IU/day – increasing to 1500-6000IU/day

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Calcium

- 32% bone mineral is calcium and 99% is stored in bone
- Peak rates of bone mineralisation 12.5years (girls) 14 years (boys)
- Data from calcium balance studies indicate net calcium balance is achieved at intakes of 1300-1500mg daily

American Consensus > 9 years 1300-1500mg/day

UK CF trust > 8 years 1300-1500mg/day

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Calcium intake and cystic fibrosis

- Calcium intake is a positive predictor of bone mineral status in adolescents (*Chan et al, 2001)*
- Calcium (1000mg) and low dose vitamin D (800IU) supplementation resulted in a reduced rate of decline in BMD at various sites (non significant). There was also a trend towards a reduction in bone turnover (*Haworth et al, 2004)*

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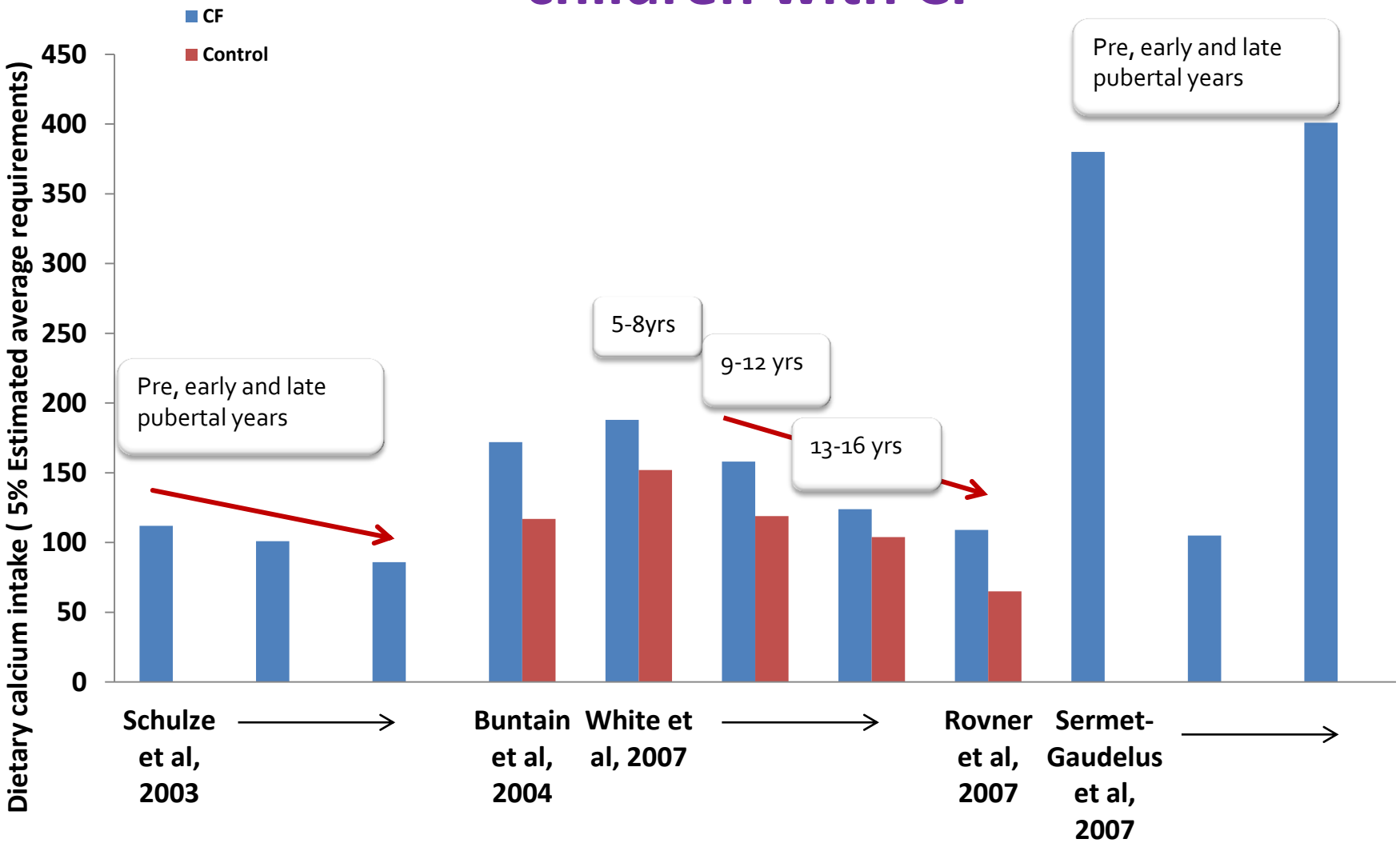
How to improve calcium status

- **Dietary calcium**
- Calcium supplements
- High plasma vitamin D to ensure optimal calcium absorption

Reported Dietary Calcium Intakes in children with CF



Calcium absorption

	Population	Pre puberty	Early puberty	Late puberty
Abrams & Stuff (1994	Healthy children	27.7%	34.4%	25%
Shulze et al, 2003	Children with CF (clinically stable, well nourished)	26.7%	39.9%	29.8%

Suggests that absorption is comparable to healthy children

Lower gut pH in CF may enhance calcium absorption

Adaptive mechanism present when Calcium intake low

Vitamin K

Deficiency

- 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

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Vitamin K supplements

Most studies support the use of phylloquinone

Europe – all pancreatic insufficient patients

Infants 0.5-2mg/day > 1 year starting dose 1-10mg/day (Sermet Gaudelus et al, 2011)

USA

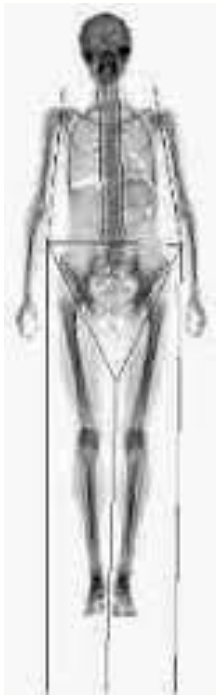
0.3-0.5mg/day (Aris et al, 2005)

UK

Babies & infants <2 years 300µg/kg/d

2-7 yrs 5mg/day /> 7 yrs 10mg/day (CF Trust, 2007)

Assessment of bone status



- Dual xray absorptiometry (not volumetric. Areal measure g/cm^2). DEXA will underestimate BMD in small individuals with short narrow bones and overestimate it for larger bones
- **Quantitative computed tomography (QCT)**
- **Quantitative Ultrasonometry**

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Quantitative sonography (QUS)

- Transmission of sound through the bone is measured
- Speed of sound decreases in osteoporotic bone
- Low cost, dedicated scanners, acquiring data mostly at the bone
- Dedicated scanners for the calcaneus, phalange and tibia are available, most at the former two

(Link ,2012)

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Advantages QUS	Challenges QUS
Shown to differentiate those with and without fragility fracture and to predict fracture risk	Doesn't assess bone quality
Diverse number of US devices, measuring and reporting variable bone parameters in different ways, examining different skeletal sites, differing levels of validation data for QUS	Lack of association with DXA measured BMD – has provided challenges
Can screen out patients with normal bone mass in CF and enable selective use of DXA (Schepper et al, 2012)	Not recommended to monitor treatment response (ISCD guidelines, 2007)

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

Initial scan age 8-10 years

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

- BMI, Vitamin D, Vitamin K and calcium play important roles in preventing low BMD
- Sensible to normalise the abnormal and correct for known risk factors
- The simultaneous presence of a number of factors has made it difficult to define the contribution of each
- Longitudinal studies are underway although early studies suggest change is slow

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Conclusions

Vit D	• Aim for 75-150nmol/l (30-60ng/ml)
Calcium	• Aim for 1300-1500mg daily > 8 years of age (assess intake annually)
Vitamin K1	• Aim for 5-10mg/day

Aim to achieve minimum of 50th BMI percentile (assess dietary energy &protein intake annually

Thank you and questions

Acknowledgements to
Sue Wolfe (Leeds Teaching Hospitals Trust)

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