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Does early nutrition program later bone health in preterm infants?

MS Fewtrell

*Childhood Nutrition Research Centre,
UCL Institute of Child Health, London*

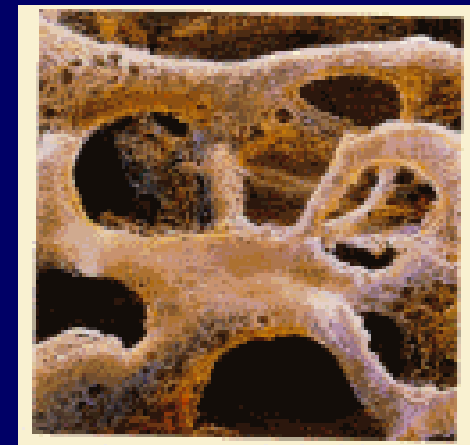
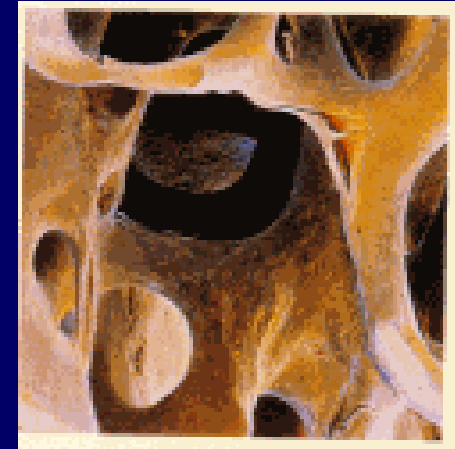


Osteoporosis

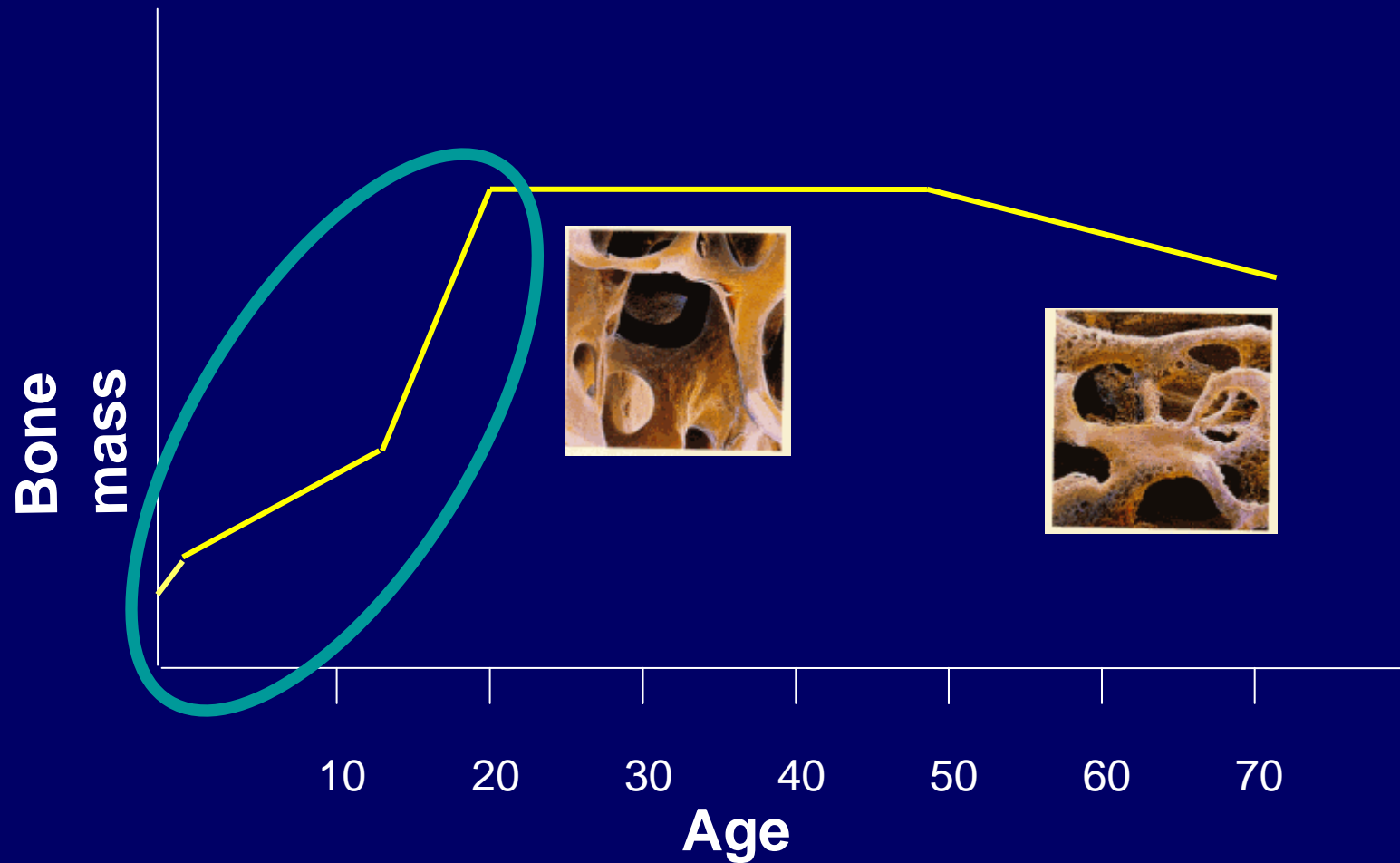
UK annual costs to NHS close to the figure for treating CVD

Lifetime risk of fracture in women similar to the risk of CVD

1/6 women sustain hip fractures – 1/9 breast cancer

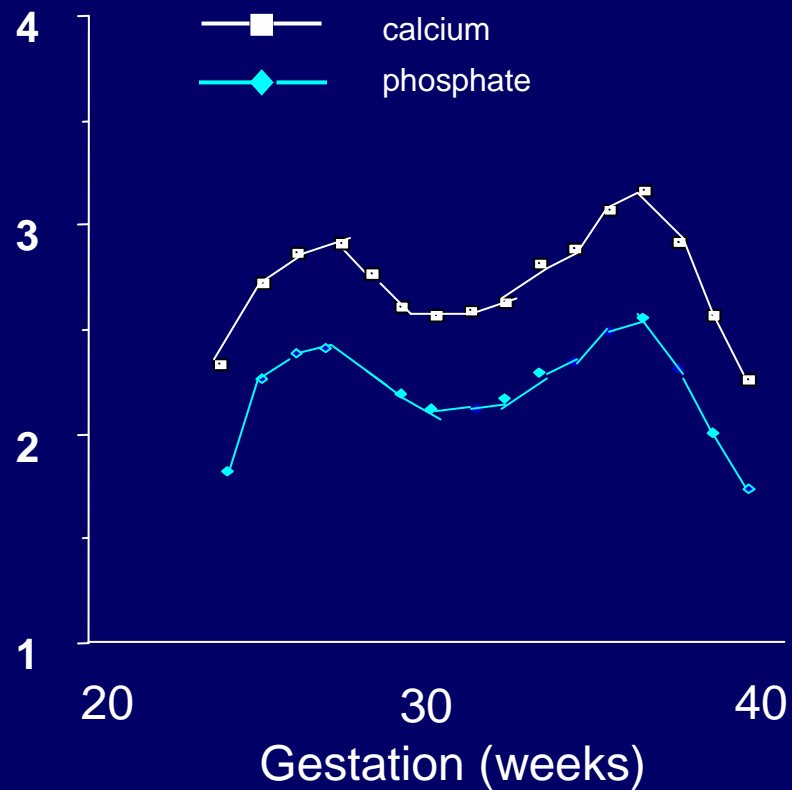


Peak bone mass



Fetal mineral accretion mmol/kg/day

90% of mineral accretion occurs during the last trimester



Metabolic bone disease of prematurity



Inadequate calcium and phosphorus intake



Undermineralised bones



Fractures

Often asymptomatic at the time

Does it have long-term consequences for bone health?

Randomised trial - recruitment 1982-85

926 infants, <1850g

Does mother want to provide breast
milk?

No
Trial 1

Yes
Trial 2

DBM v PTF

*Cambridge
Ipswich
Kings Lynn*

DBM+MBM v PTF+MBM

TF v PTF

*Norwich
Sheffield*

TF+MBM v PTF+MBM

Composition of trial diets

	PTF	TF	DBM	MBM	<i>Modern preterm formula</i>
Protein (g/dl)	2.0	1.5	1.3	1.5	2.4
Energy (kcal/dl)	80	68	<50	62	80
Fat (g/dl)	4.9	3.8	2.0	3.0	4.4
Calcium (mg/dl)	70	35	30	30	100
Phosphorus (mg/dl)	35	29	17	14	50

Neonatal mineral intakes mg/kg/day

	DBM	PTF	p
<i>Phosphorus</i>	23.1 (6.2)	32.0 (13.9)	<0.001
<i>Calcium</i>	46.2 (7.7)	66.4 (24.6)	<0.001
<i>Peak ALP</i>	992 (570)	766 (401)	0.013

Current recommended intakes:

>120mg/kg/day for calcium

>62mg/kg/day for phosphorus

Follow-up studies

5 years

- Higher bone mass in subjects with greater neonatal consumption of human milk

10 -12 years

- No effect of neonatal diet on bone mass
- Higher osteocalcin in subjects who received lower nutrient diets

Early diet and peak bone mass: 20 year follow-up of a randomised trial in preterm infants

MS Fewtrell, JE Williams, A Singhal,
PR Murgatroyd, N Fuller, A Lucas

*Childhood Nutrition Research Centre, UCL Institute of Child Health, London
Addenbrooke's Clinical Research Centre, Cambridge*

Fewtrell et al. Bone 2009;45:142

20 year follow-up - hypotheses

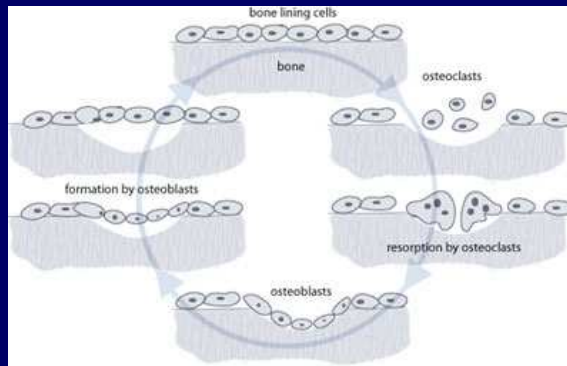
1. Early diet programs peak bone mass and bone turnover
2. Human milk has a specific enhancing effect on peak bone mass
3. Preterm subjects have lower peak bone mass compared to population reference data

Outcome measures



DXA

Bone mass at whole body, hip, lumbar spine



Bone turnover

Formation Osteocalcin

P1NP

BSALP

Resorption CTX

Hypothesis 1: Effect of randomised diet

No effect of randomised diet on

- Weight
- Height
- Bone mass at any skeletal site
- Bone turnover

Hypothesis 2: Effect of human milk

Randomised comparison of DBM v PTF (n=13 v 12)

No significant difference in bone mass or turnover

DBM group had higher values.....

WB bone area 5.7%

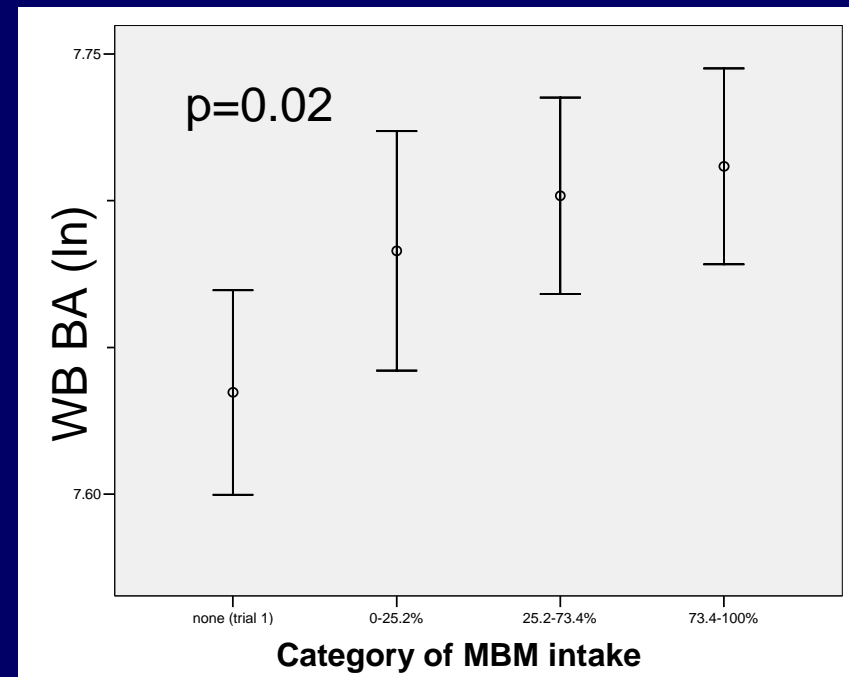
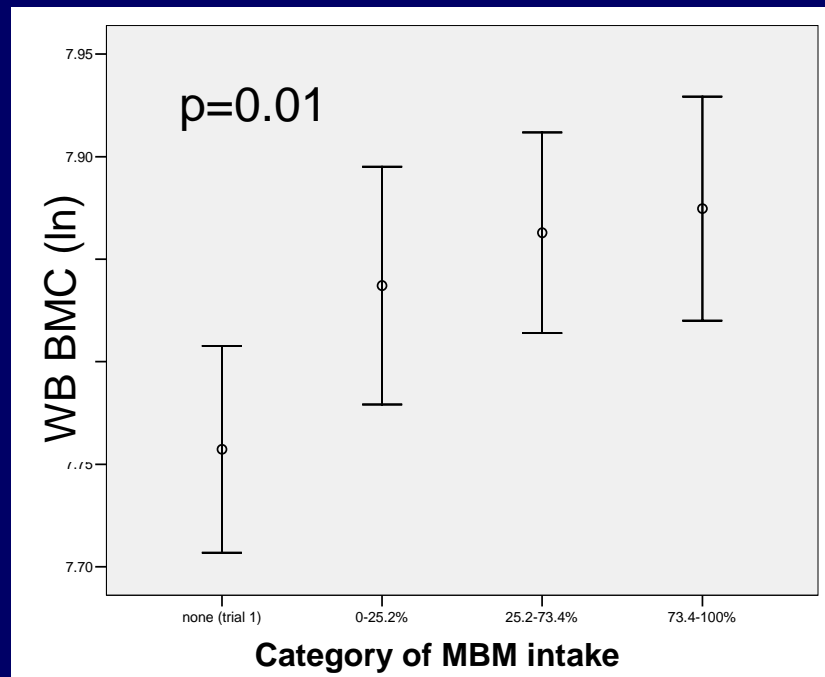
WB BMC 6%

LS bone area 8.6%

LS BMC 7.7%

Human milk
Non-randomised analyses

Dose response relationship between whole body BMC and BA and the amount of MBM received during the neonatal period



No association between %MBM and later height or weight

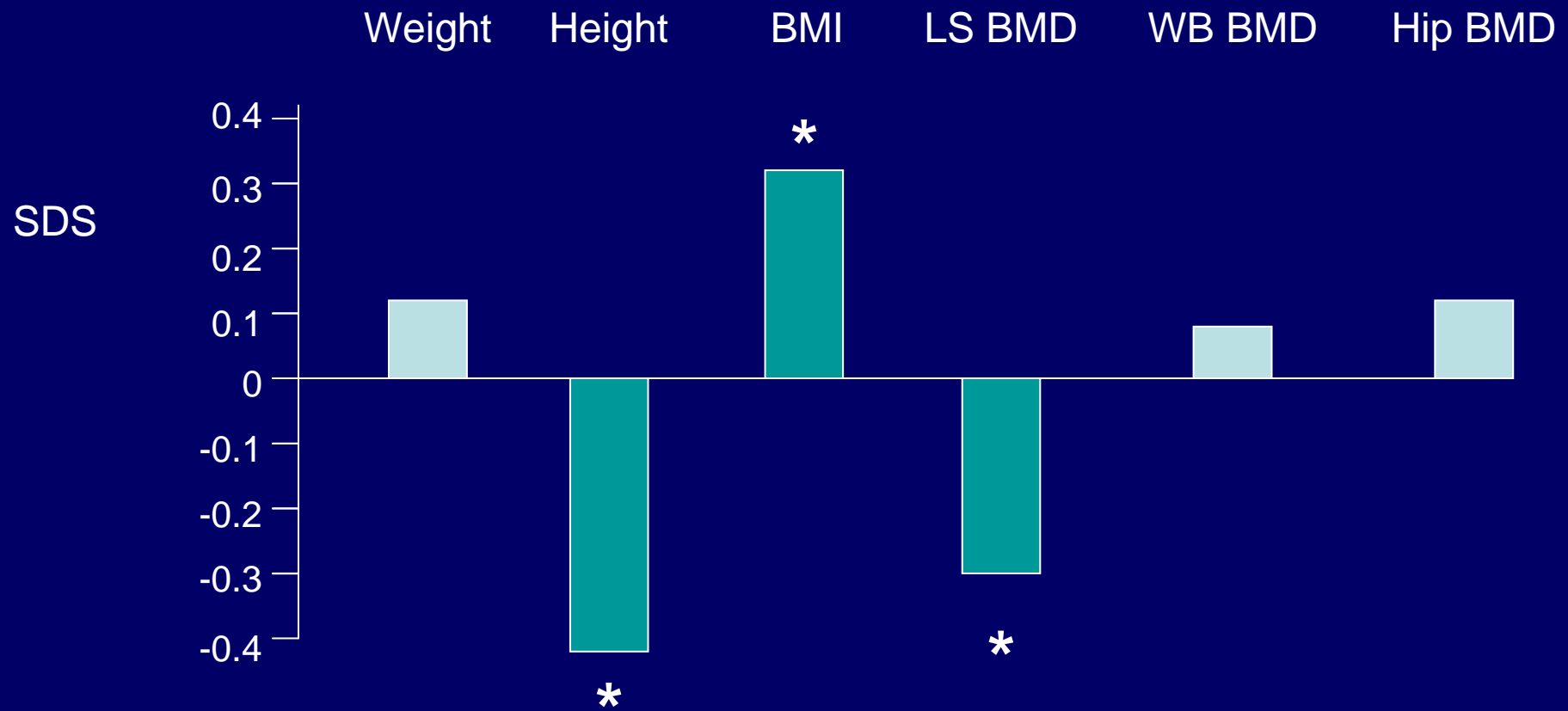
'Low' versus 'High' human milk

Higher WB BA and BMC in 'high' human milk group

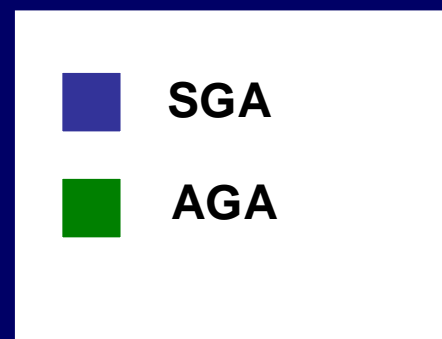
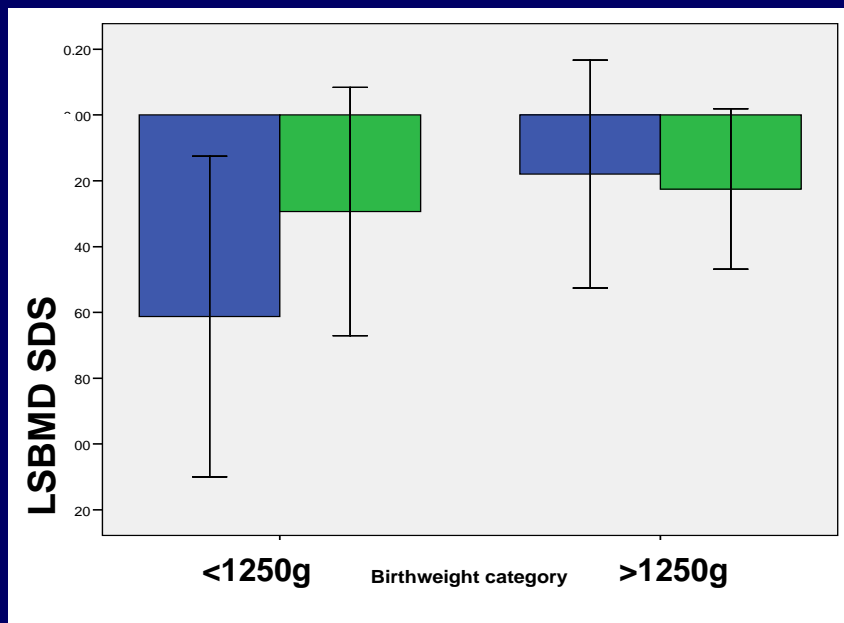
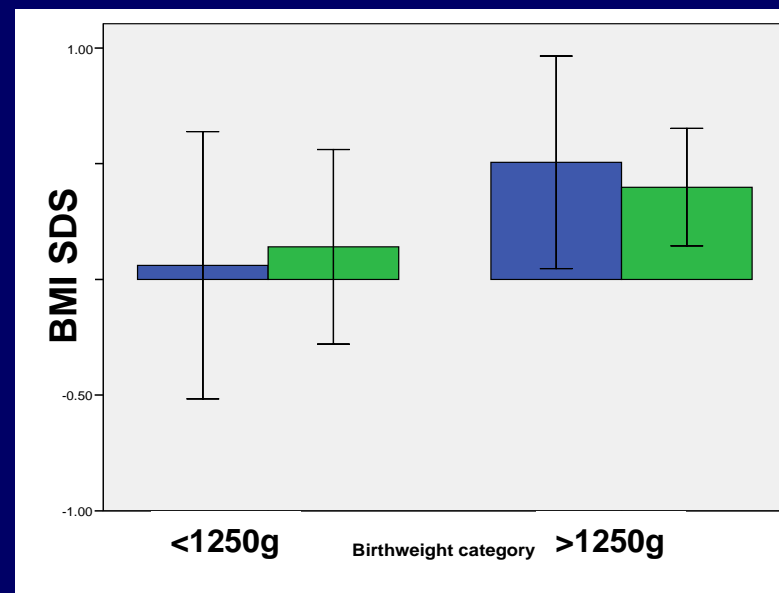
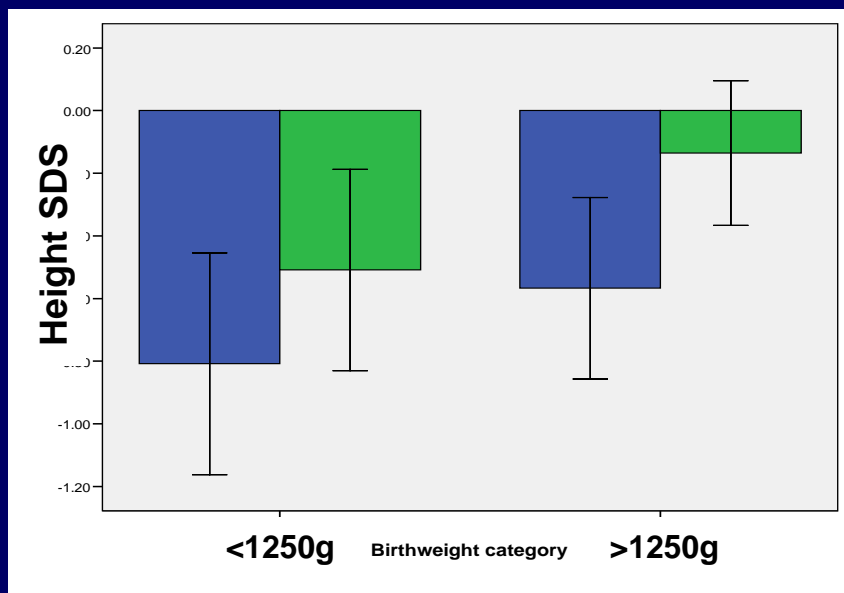
BA 3.5% (p=0.01)

BMC 4.8% (p=0.03)

Hypothesis 3: Peak bone mass in subjects born preterm compared to population reference data



Height, BMI and lumbar spine BMD in preterm infants at 20 years



Fractures

32% reported at least one fracture

No effect of randomised diet on % with fracture

No difference in bone mass between those with and without fractures

Which factors predict skeletal size and bone mass in early adult life?

Greater whole body bone size and bone mineralisation predicted by

- Greater current weight and height
- Higher neonatal human milk intake
- Greater height SD score at age 7
- Lower relative height gain from 7-20 years

Summary

1. Early randomised diet had no effect on later bone mass or turnover - despite large differences in early nutritional intake

Lower height and LS BMD in this cohort may not be directly related to sub-optimal mineral intake

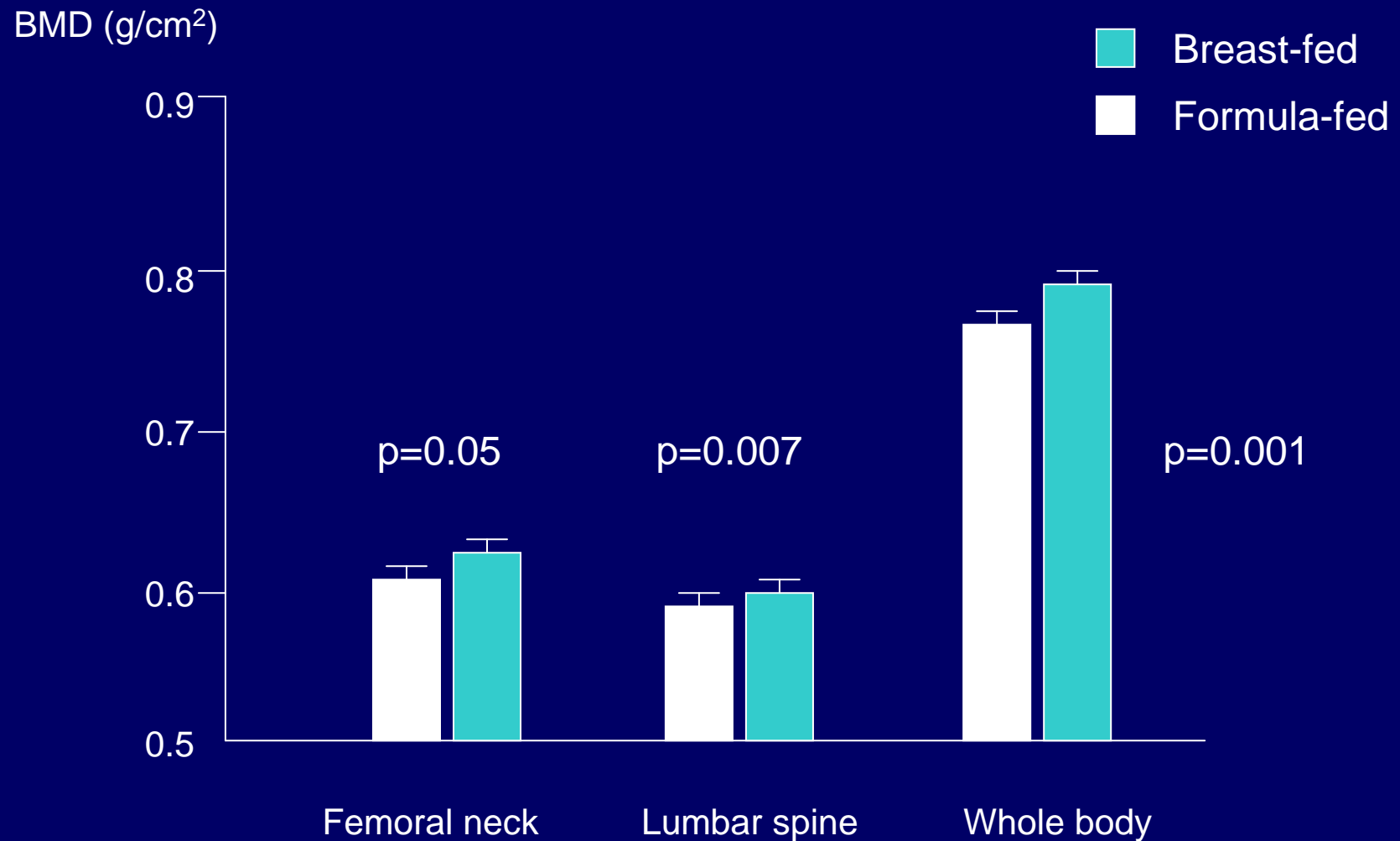
? other effects of prematurity

Summary

2. Human milk is associated with higher bone size and bone mass - despite its low nutrient and mineral content

? Non-nutrient factors in breast milk

Breastfeeding and childhood bone mass in term infants



Study strengths and weaknesses

Unique RCT with long-term follow-up

BUT must consider

Attrition – study power, bias

Generalisability to modern neonates

Differences between diet groups were much greater than would occur in a modern NICU

- No mineral supplements
- No breast milk fortifiers
- All infants received vitamin D 800IU per day

Current recommended mineral intakes for preterm infants are high and difficult to meet especially using parenteral nutrition

Are these high mineral intakes necessary for bone health?

Attempts to meet mineral requirements using parenteral nutrition solutions results in exposure to aluminium

Neonatal aluminium exposure and later bone health

- no known biological function
- accumulates in the body if
 - high exposure
 - GI tract bypassed
 - poor renal function
- preterm infants are exposed via *parenteral nutrition* – especially *calcium gluconate*

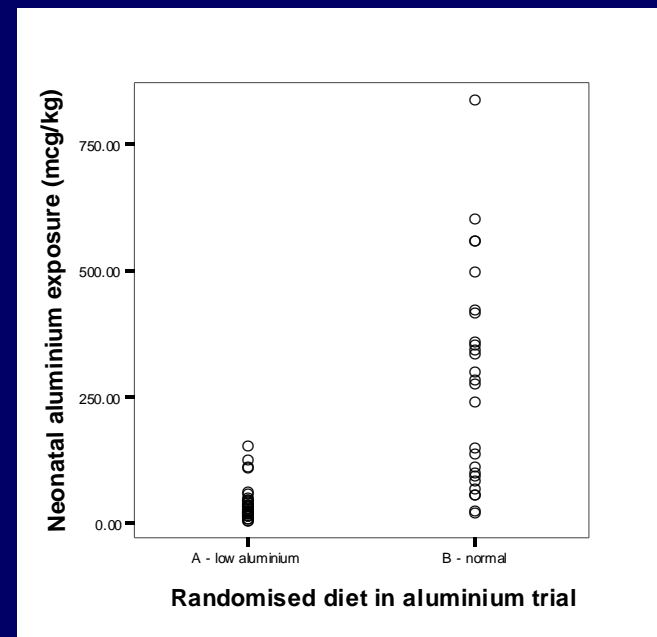
Randomised trial of standard versus aluminium-depleted PN solution in preterm infants

Standard

Aluminium-depleted
(AD)

Calcium gluconate
K acid phosphate

Calcium chloride
Na-K phosphate



Bone mass at age 15

- Lumbar spine BMC 0.7SD higher in AD group
- Hip BMC significantly lower (7%) in subjects with aluminium exposure >median, independent of body size

Aluminium exposure may adversely programme bone health

Relevant to contemporary infants – still exposed to aluminium via PN – especially from attempts to achieve high mineral intakes

Impossible to significantly reduce exposure with currently available solutions

Conclusions

1. Remarkably little apparent effect of early nutrient or mineral intake on later bone healthmodern neonates have a much higher mineral intake
2. Human milk associated with higher whole body bone mass and larger bones – potentially beneficial long-term

Acknowledgements

Subjects and families

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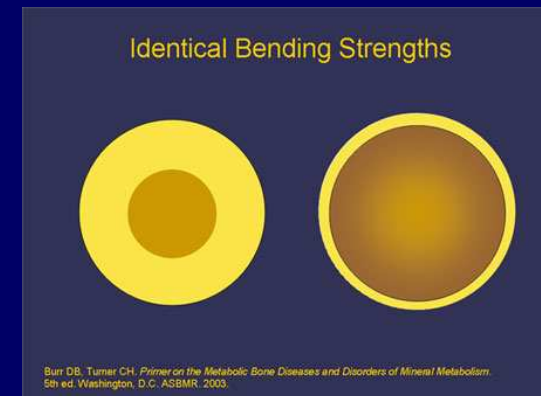




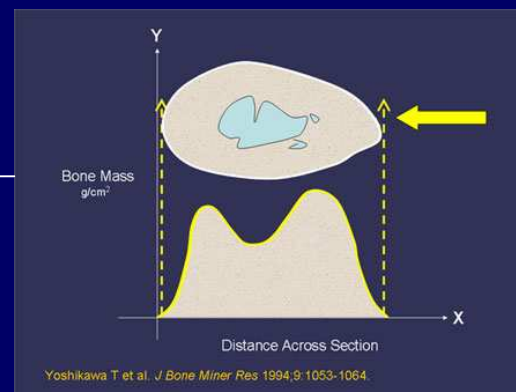
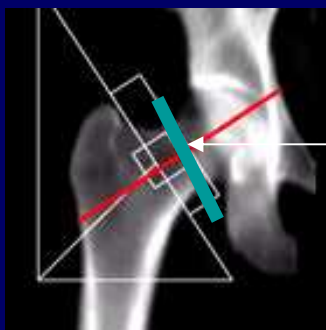
Assessment of bone strength and geometry

Bone strength and resistance to bending and compression depends on

- material properties (mineral content)
- distribution of the mineral
- geometry of the bone



These parameters can be measured on DXA hip scans



Factors relating to hip strength in early adult life

Greater hip strength parameters predicted by

- Greater current weight and height
- Higher femoral neck BMC
- Lower relative height gain from 7-20 years

No effect of neonatal nutrition or MBD on measures of hip geometry or strength – including Hip Axis Length

No differences in hip bone mass or geometry between those with and without previous fractures