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Insights into Programming of Bone Development from the ALSPAC Cohort

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Summary

- Introduction
 - » Possible factors involved in skeletal programming
 - » Summary of the ALSPAC cohort
- Use of ALSPAC to investigate skeletal programming



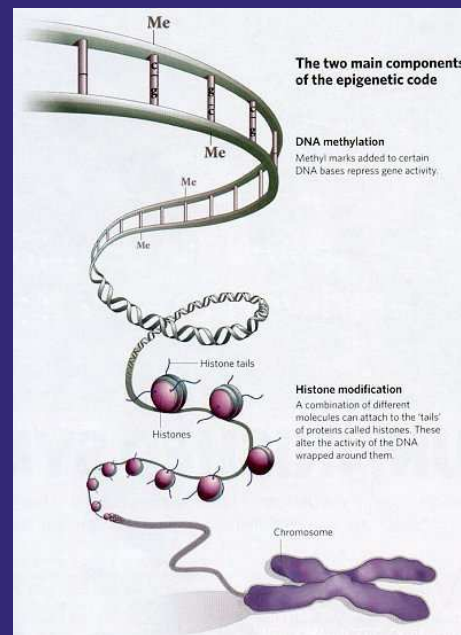
Factors Which May Play a Role the Programming of Bone Development

- Birth weight as a proxy measure for general nutrition in utero
 - » Birth weight predicts bone size in young adulthood at cortical sites in men and trabecular sites in women from The Gambia. S De Bono et al 2010 Bone 46: 1316-21



Factors Which May Play a Role the Programming of Bone Development

- Specific nutritional factors in utero
 - » Maternal dietary intake of methyl donors eg methionine, choline and folate



Factors Which May Play a Role the Programming of Bone Development

- Specific nutritional factors in utero
 - » Maternal folate intake
 - » Maternal vitamin D intake
 - Pleiotrophic effects of vitamin D on development
 - Vitamin D may regulate transcription of methyltransferase genes (Kim et al 2009 Nature 461:1007-1012)
 - Reported associations between maternal vitamin D status and DXA of the child at age nine (MK Javaid et al 2006 Lancet 367:36-43)



Factors Which May Play a Role the Programming of Bone Development

- Other environmental factors operating in utero
 - » Maternal smoking
 - Women who smoked had infants with a lower BMC and BMD (K Godfrey et al 2001 J Bone Miner Res 16: 1694-03)



Avon Longitudinal Study of Parents and Children (ALSPAC)

- Geographically based birth cohort to which pregnant women residing in Avon were recruited 1991-2.
- Approximately 14,000 women and children were enrolled.
- Information is obtained from questionnaires administered from pregnancy and throughout childhood, and from 'hands-on' assessment clinics.



Bone Measures in ALSPAC

Measured at clinics:



DXA scan at:

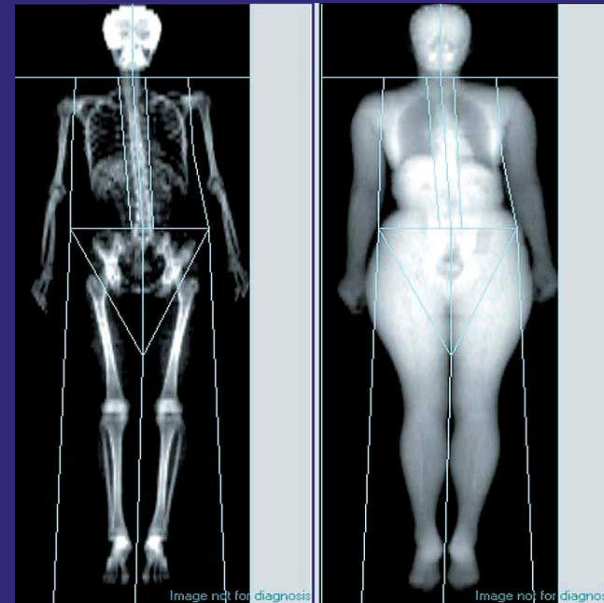
9 years
11 years
13 years
15 years
17 years



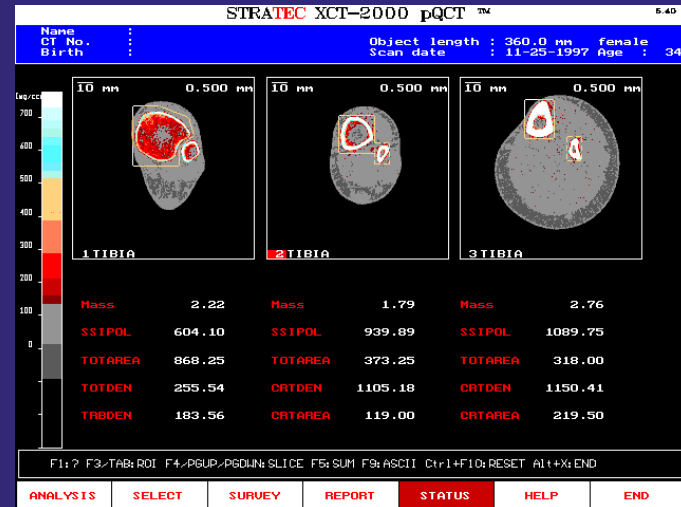
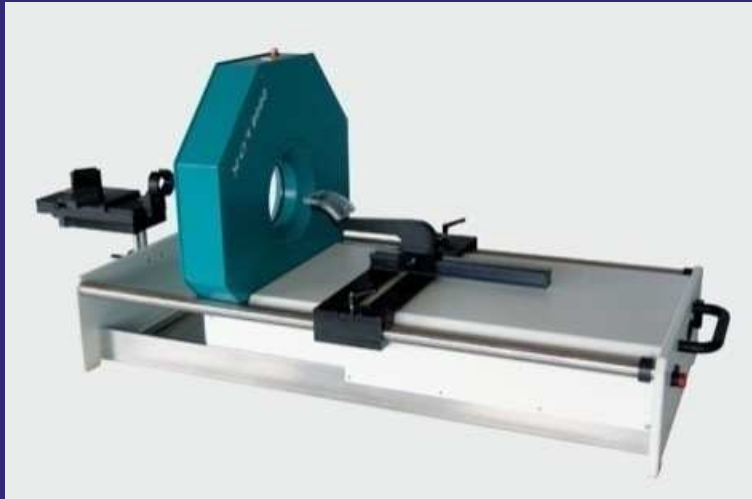
pQCT scan at:
15 years
17 years



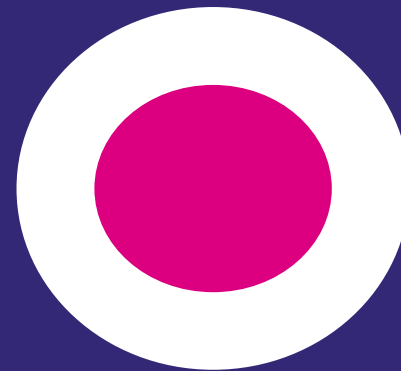
Using DXA Scans to Measure Whole Body and Spinal Bone Mineral Content (BMC) and Density (BMD)



Measurements of cortical bone at the mid tibia by pQCT



Cortical BMC
Periosteal circumference
Cortical thickness
Cortical BMD



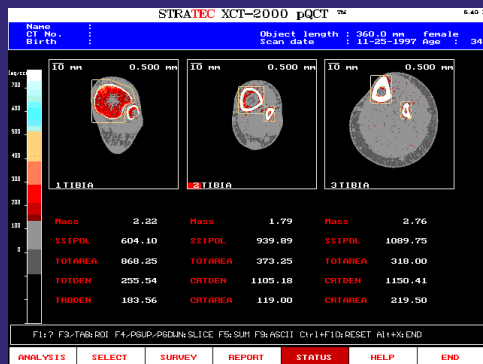
Summary

- Introduction
- Use of ALSPAC to investigate skeletal programming
 - » Birth weight and bone development
 - » Maternal folate and bone development
 - » Maternal vitamin D and bone development
 - » Maternal smoking and bone development

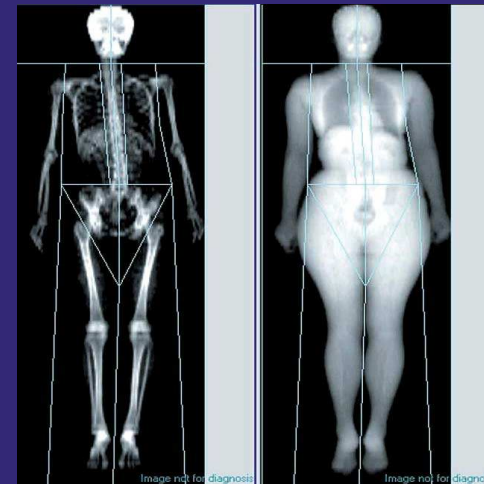


Is birth weight related to bone development of the child?

Birth weight



pQCT scans at 15



Total body DXA age 9

We examined relationships birth weight and total body DXA (age 9) and pQCT scans (age 15) adjusting for a range of possible confounders



Birth Weight and Total Body Bone Mass as Measured by DXA At Age Nine (N=6876)

	Model	Beta	95% CI	P
Height	Basic*	0.54	0.49, 0.59	<0.001
Weight	Basic*	0.46	0.41, 0.51	<0.001
BMC	Basic*	0.46	0.41, 0.51	<0.001

*Gender, age at DXA, gestation



Birth Weight and Total Body Bone Mass as Measured by DXA At Age Nine (N=6876)

	Model	Beta	95% CI	P
BMC	Basic*	0.46	0.41, 0.51	<0.001
BMC	+parental ht & wt	0.24	0.18, 0.30	<0.001
BMC	+stress factors**	0.25	0.19, 0.31	<0.001
BMC	+ht & wt at age 9	-0.02	-0.05, 0.01	0.2
BMC	Bone area	-0.22	-0.27, -0.16	<0.001

*Gender, age at DXA, gestation

**Maternal education, smoking in pregnancy, family adversity



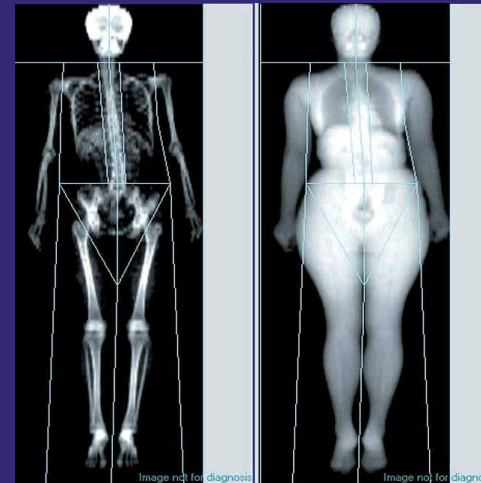
Interim Conclusions (1/4)

- In minimally adjusted analyses, birth weight is positively related to total body BMC at age 9 and to cortical bone mass at age 15.
- These associations reflect shared relationships with body size, as they were lost after adjusting for parental and child height and weight.
- After adjusting for body size, birth weight was inversely related to cortical thickness and density, suggesting intrauterine nutrition per se may adversely affect on cortical bone development.



Is maternal diet related to bone development of the child?

Maternal diet, including folate intake, was assessed by food frequency questionnaire in the third trimester

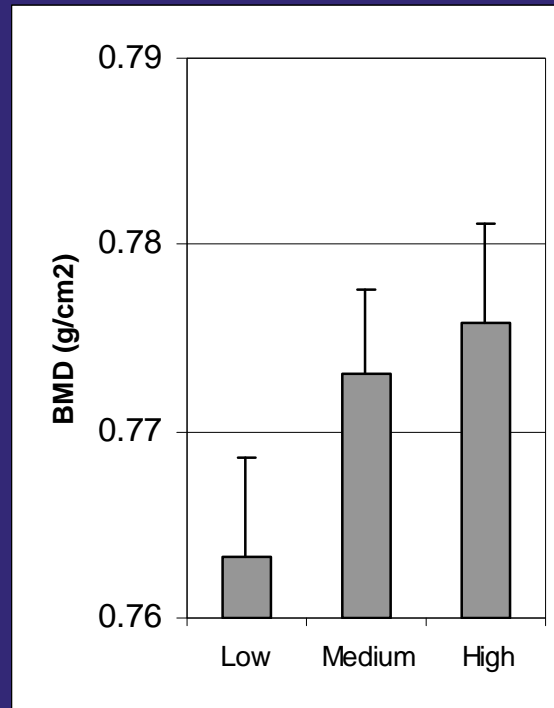


Total body DXA age 9

We examined associations between maternal dietary constituents and total body and spinal BMD, adjusted for total energy intake



Maternal folate intake and spinal BMD of the child at age nine Tobias JH et al 2005, OI 16:1731



Spinal BMD according to tertile of maternal folate intake. Results show means and 95% CI (n=2540). F-test revealed significant difference between tertiles ($p = 0.02$).



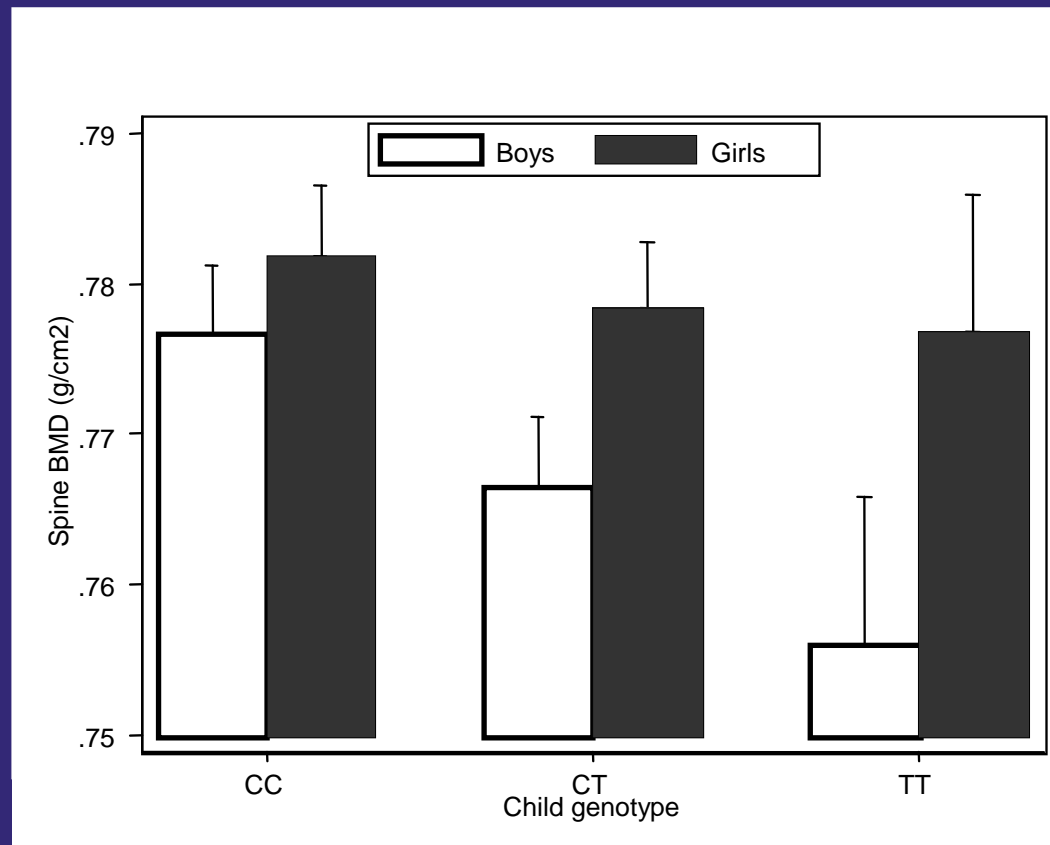
Methylenetetrahydrofolate reductase (MTHFR)

- Associations between maternal diet and BMD of the child could reflect confounding eg via shared relationships with diet of the child.
- MTHFR is involved in folate metabolism, and mediates effects of dietary folate levels on availability of methyl groups for DNA methylation.
 - » The T (minor) allele of the C677T MTHFR polymorphism is associated with decreased levels of folate and DNA methylation.
- Does MTHFR genotype of the mother affect BMD of the child independently of genotype of the child?



Spinal BMD According to MTHFR

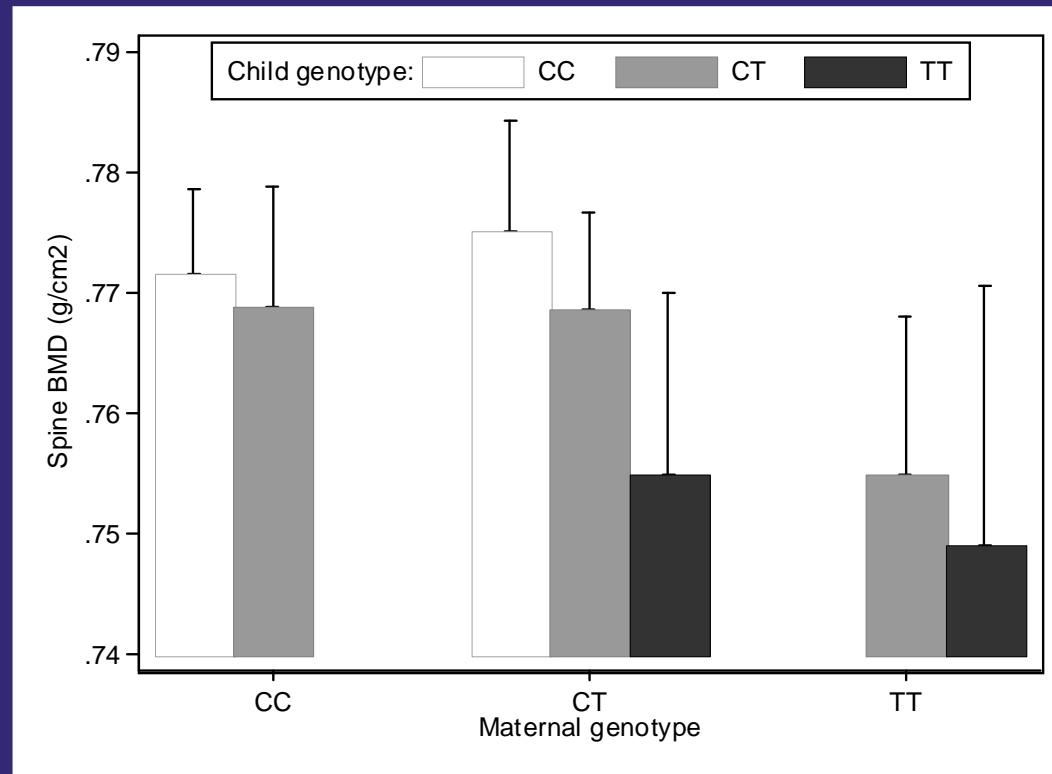
Genotype C Steer et al 2009 J Bone Miner Res: 24:117-124



Graphs show mean + 95% confidence intervals



Maternal MTHFR Genotype Affects Spinal BMD Independently of Child's Genotype (1015 boys)



Graphs show mean + 95% confidence intervals

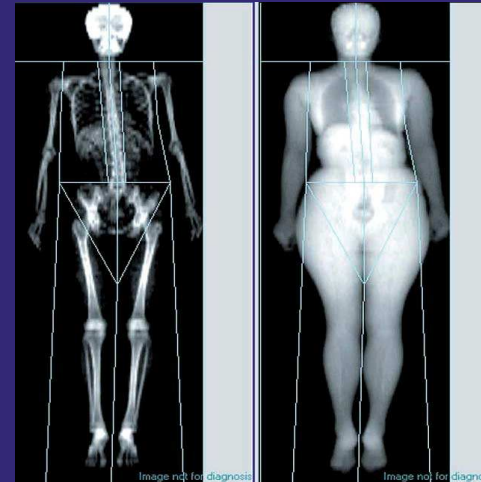
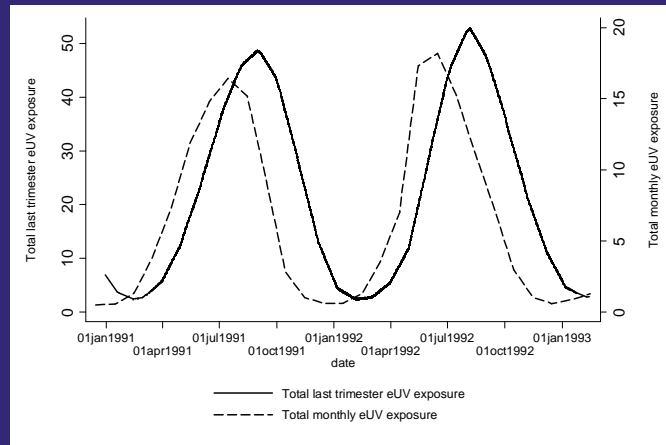


Interim Conclusions (2/4)

- Maternal folate intake is positively related to spinal BMD at age nine.
- Maternal MTHFR genotype associated with lower folate levels are negatively related to spinal BMD at age nine independently of child genotype (boys only).
- Maternal folate status may have an independent effect on bone development of the child.



Is background UVB in pregnancy related to bone development of the child?

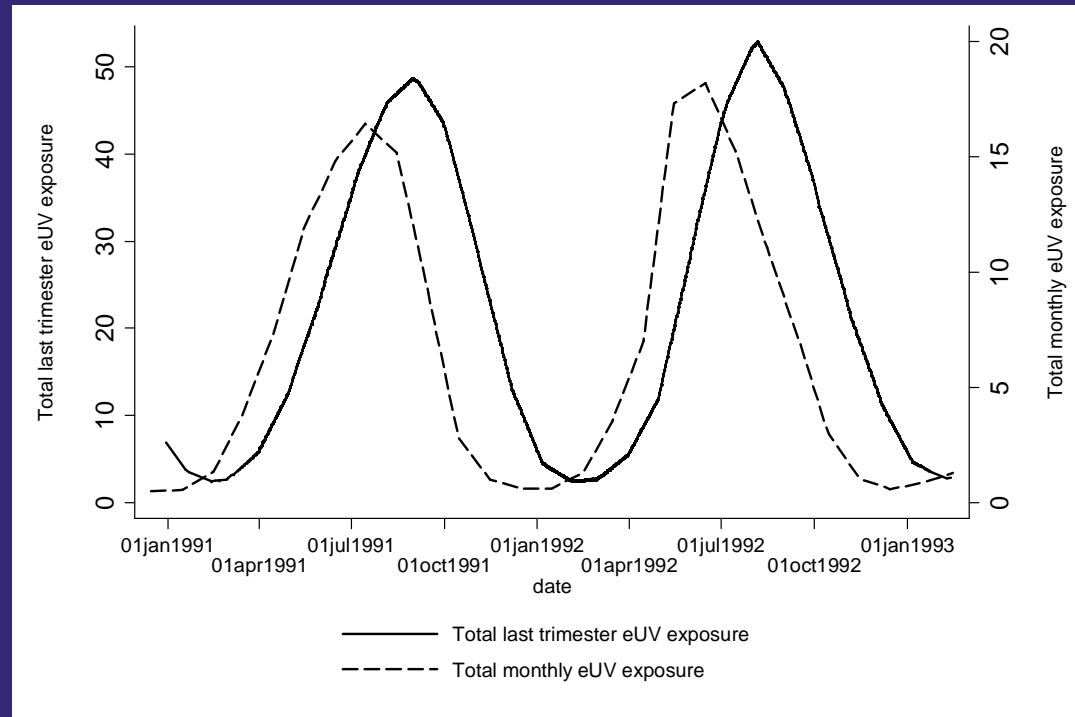


We examined the relationship between background UVB in the third trimester of pregnancy, and whole body DXA scan results at age 9 in 6995 children



Predicting third trimester Ultraviolet light exposure from sunlight records

Sayers et al 2009 Int J Epid 38:1681-8

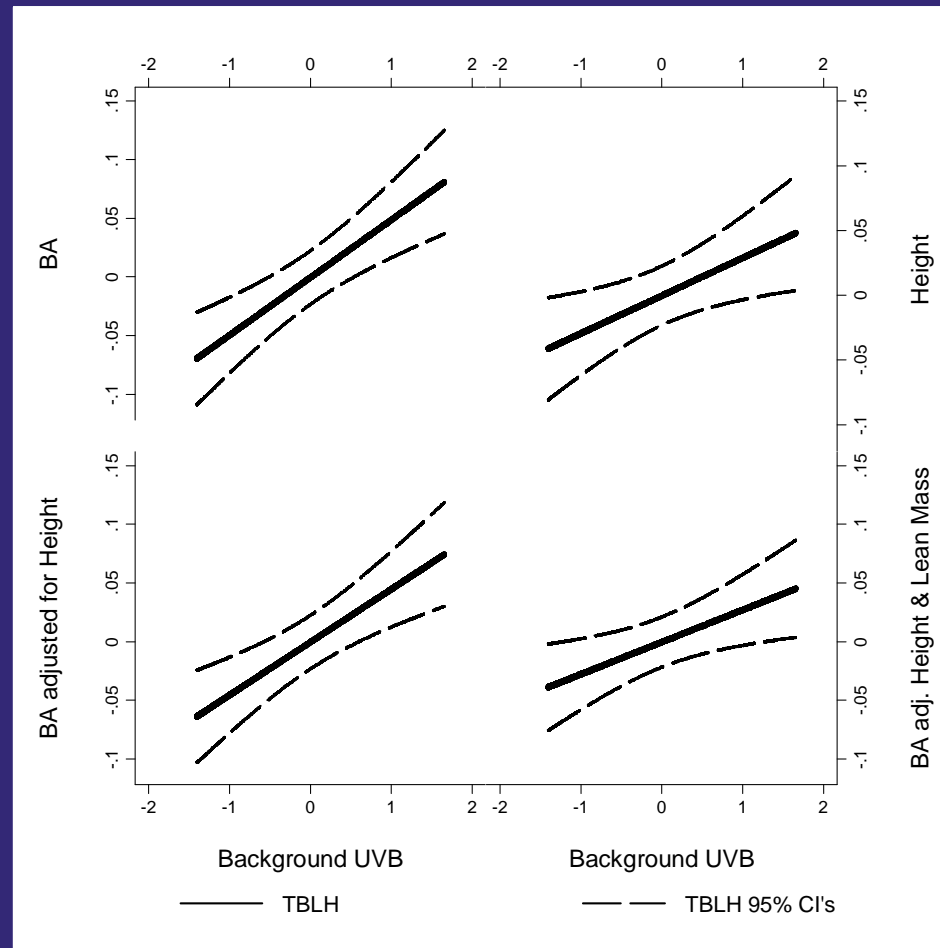


Serum total 25-hydroxyvitamin D, measured at 36 weeks gestation in a subgroup of 355 study mothers, versus estimated background UVB in the third trimester

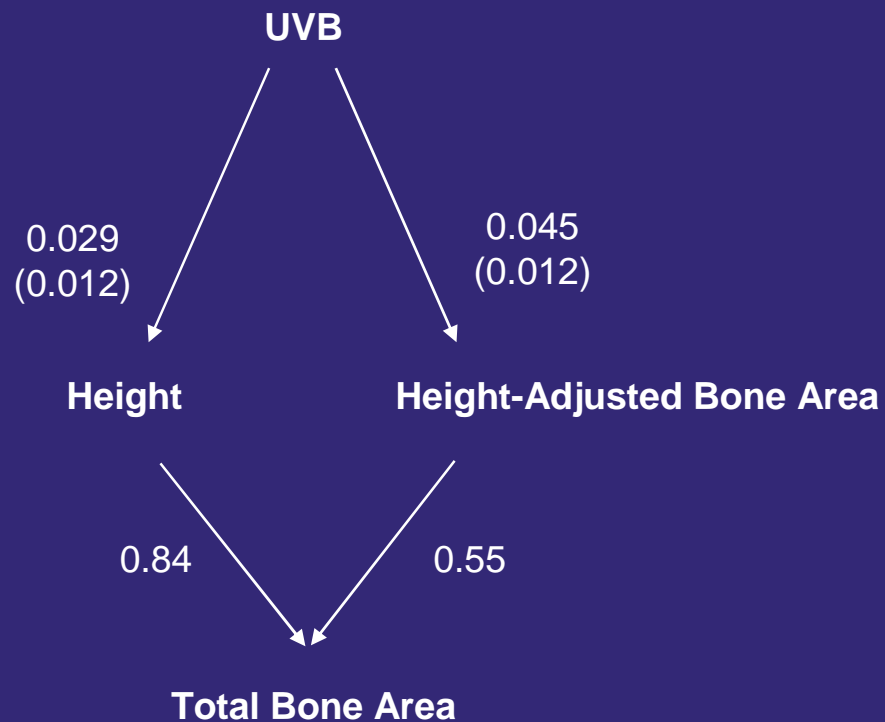


Ultraviolet light in pregnancy affects bone size of the child

A Sayers et al 2009 J Clin Endo Metab: 94: 765 - 771



Maternal UVB and bone development of the child: Path analysis



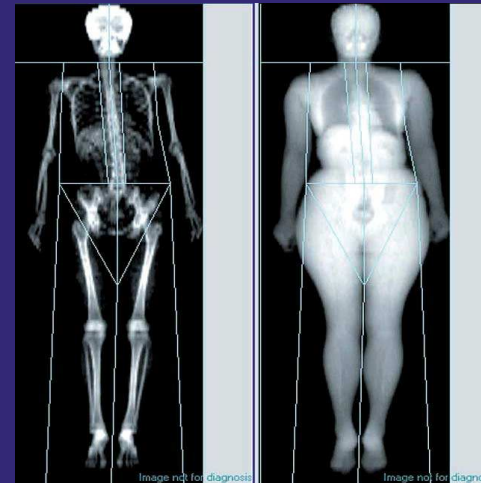
Interim Conclusions (3/4)

- Background UVB levels during the third trimester of pregnancy are positively related to bone size of the child, which may reflect an influence of maternal vitamin D status.
- Although background UVB was also related to height, this did not entirely explain the association with bone size.
- Our results are consistent with an effect of maternal UVB on periosteal (ie outwards) growth of the skeleton in childhood.



Is parental smoking during pregnancy related to bone development of the child?

Maternal and paternal smoking was assessed during pregnancy by questionnaire



Total body DXA age 9

We examined the relationship between maternal and paternal smoking during pregnancy, and total body and spinal DXA results as measured in the child at age nine



Interim Conclusions (4/4)

- Maternal smoking during pregnancy was positively associated with bone mass in girls but was not associated with bone mass in boys.
- Maternal and paternal associations were of similar sizes, with no statistical evidence for differences for any of the bone outcomes studied.
- All relationships attenuated to the null on adjustment for the child's height and weight at the time of the DXA scan, and were driven mainly by the child's weight.
- The relationships found are likely to be explained by familial characteristics related to childhood adiposity rather than an intrauterine effect.



Summary

- After correcting for parental and child size, general nutrition in utero as reflected by birth weight was inversely related to cortical thickness and density.
- Maternal folate intake and MTHFR genotype were both related to spinal BMD at age nine.
- Background UVB during the third trimester of pregnancy was positively related to bone size at age nine even after adjusting for height.
- In adjusted models, no relation was observed between maternal smoking during pregnancy and bone development.



Discussion

- Specific nutritional factors during pregnancy such as folate and vitamin D may influence bone development of the child, possibly reflecting effects on DNA methylation.
- Intake of folate supplements was not related to BMD measures in childhood; maternal folate and UVB were related to differing aspects of skeletal development which goes against a common pathway.
- Further studies are justified to examine the role of altered DNA methylation in utero in programming subsequent bone development.



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