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LETTER

Vitamin D and bone development

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Dear Editor,

We thank Dr Sugiyama and colleagues for their comments [1] on our recent review on the role of vitamin D status in bone health during growth [2], and read with great interest their hypothesis relating to potential mechanisms.

As Sugiyama et al. suggest, there are complex relationships among bone mineral density (BMD), bone size, bone strength and fracture risk in children. Indeed, physical activity has been positively associated with both measures of bone size and density in children [3, 4], yet is also associated with increased fracture risk in childhood [5]. The mechanostat theory recognises that muscular strains stimulate bone modelling and mineralisation [6]; however, more active children are also likely to have greater exposure to potential fracture-causing events. It is possible that a similar explanation also confounds associations between childhood vitamin D status and fracture occurrence: children following sedentary indoor lifestyles are more likely to have lower serum 25-hydroxyvitamin D [25(OH)D], but also limited exposure to high fracture risk activities compared with more active children, independent of any, as yet unclear, effects on bone mass and geometry. Furthermore, to date all studies of vitamin D supplementation in children have assessed areal BMD using dual energy X-ray absorptiometry [2], thus limiting inferences, as suggested by Sugiyama et al., relating to the importance of differential effects on size, geometry or density. One randomised controlled trial of vitamin D and calcium supplementation for 6 months in peripubertal girls did demonstrate higher volumetric BMD, trabecular and cortical area assessed using peripheral quantitative computed tomography (pQCT) in the supplemented group [7].

In contrast with the evidence in postnatal life, several, but not all, studies have shown associations between maternal antenatal 25(OH)D and offspring bone and body composition [8–11]. We have recently documented further evidence that maternal gestational 25(OH)D deficiency is associated with impaired offspring bone development. In the Southampton Women's Survey (SWS), a prospective UK mother-offspring cohort [12], maternal serum 25(OH)D was assessed using radioimmunoassay (Diasorin) at 34 weeks gestation. At 6–7 years of age, their children underwent DXA scanning (Hologic Discovery, Hologic Inc, Bedford, USA), yielding measures at whole body less head [WBLH] (n=1004) and lumbar spine [LS] (n=1030) sites. Offspring of mothers who had 25(OH)D<25 nmol/l in late pregnancy had lower WBLH bone area, BMC and areal bone mineral density (aBMD), and lumbar spine BMC, at age 6 years compared to offspring of mothers who were vitamin D replete (Fig. 1). These differences remained statistically significant after adjustment for maternal age, ethnicity, height, pre-pregnancy BMI,

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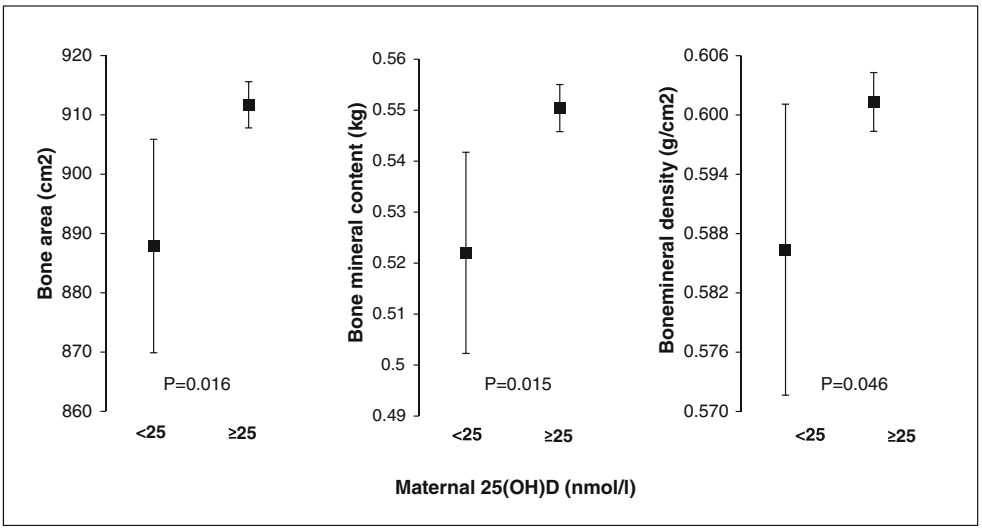

Fig. 1 Whole body less head bone area, bone mineral content and bone mineral density at 6–7 years of age according to maternal 25(OH)D status in late pregnancy Shown as mean ±95 % confidence interval

smoking in late pregnancy, social class, maternal educational attainment and duration of breast feeding (Table 1). Future work is needed to determine whether prenatally 25(OH)D has a direct action on bone, or if this effect is mediated through higher muscular strains, as we have previously demonstrated positive associations between maternal 25(OH)D and offspring muscle strength in childhood [13].

In conclusion, it is clear that elucidation of any differential effects of vitamin D status or supplementation on bone size, geometry and density, as suggested by Sugiyama et al., will require use of appropriate three-dimensional modalities such as pQCT. Given the complexity of potential confounding and reverse causality in observational studies relating vitamin D to any clinical outcome [13], these effects may be best investigated in the context of high quality intervention studies [14]; indeed such an approach will be essential for the appropriate formulation of strategies aimed at optimising bone health across the lifecourse.

Table 1 Adjusted mean difference (95 % confidence interval) in bone mineralisation at age 6 years in children born to mothers with 25(OH)D< 25 nmol/l in late pregnancy compared to those with a 25(OH)D above this threshold

	Whole body less head	Lumbar spine
Bone area (cm^2)	−26.0 (−45.5, −6.5)**	−0.8 (−1.7, 0.10)
Bone mineral content (g)	−30.8 (−53.8, −7.7)**	−1.0 (−1.8, −0.2)*
Areal bone mineral density (g/cm^2)	−0.016 (−0.031, −0.001)*	−0.016 (−0.035, 0.002)

Adjusted for maternal age, ethnicity, height, pre-pregnancy BMI, smoking in late pregnancy, social class, maternal educational attainment and duration of breast feeding

*$p<0.05$; **$p<0.01$

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