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Similar maternal and paternal relationships with offspring bone mass do not exclude an intrauterine mechanism: Evidence from Southampton Women's Survey

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In their recent paper, McDonald-Wallis et al.(1) found that maternal and paternal smoking before pregnancy were related similarly to offspring bone mass at age 10 years. The authors concluded, as in their earlier paper with parental BMI as the predictor(2), that their findings did not support an intra-uterine mechanism, but were mediated by genetic and postnatal environmental factors. We would like to offer an alternative view.

We examined the associations between parental smoking and offspring bone indices, assessed by DXA at birth in the Southampton Women's Survey(3), an ongoing prospective mother-offspring cohort including detailed characterisation of the women before and during pregnancy. The mean whole body bone mineral content (BMC) at birth of babies born to mothers who smoked in pregnancy was 4.1g lower than that of babies of non-smokers($p=0.002$); in contrast the difference by paternal smoking was small and not statistically significant(-0.05g , $p=0.98$). Additionally, maternal pre-pregnancy BMI was positively associated with offspring whole body BMC at birth($\beta=11.9\text{g per kg/m}^2$, $p<0.001$) but no relationship was observed for paternal BMI($\beta=1.2\text{g per kg/m}^2$, $p=0.81$). These results clearly demonstrate a specific maternal, intrauterine effect on BMC at birth. Indeed, in the papers by MacDonald-Wallis et al., the associations by parent were similar when the imputed dataset was used, but stronger maternal than paternal-child relationships were observed when the un-imputed dataset was analysed. The authors provide a rationale for why the imputed dataset might be preferred, but clearly the use of imputation lends a degree of uncertainty as to the conclusions drawn.

There is likely to be co-linearity between environmental factors present before, during and after pregnancy, influencing mother, father and child, and complicating assessment of the time point(s) at which the biological effect is most important. We found that the lifestyle and health behaviour of women planning a pregnancy is very similar to that of women not aiming to conceive(4). Additionally we have observed strong correlations between maternal triceps skinfold thickness before and during pregnancy (5;6); although women may give up smoking whilst pregnant(7), this abstinence may not continue postnatally, and women who smoke during pregnancy are likely to be those with a long-term commitment to the habit. We therefore suggest that, because some environmental influences are likely to be similar before, during and after pregnancy, the statistical and experimental designs employed by

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cohort studies without detailed perinatal body composition data do not allow us to be sure that the biological effect is in post-natal and not intra-uterine life. The positive relationship between birthweight and adult BMC, confirmed by a recent meta-analysis(8), does suggest that there is at least some scope for long term modulation of bone mineral accrual originating in the intra-uterine period.

Finally it is clear that environmental factors are an important influence on bone development, whether acting before, during, or soon after pregnancy. Given the small proportion of the variance in bone mineral density explained by genotype in several genome-wide association studies(9;10), results from ALSPAC, SWS and other cohorts emphasize the need to address optimisation of bone mass throughout the lifecourse.

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