Relation of maternal prepregnancy body mass index with offspring bone mass in childhood: is there evidence for an intrauterine effect?1–4

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ABSTRACT

Background: Evidence indicates that intrauterine skeletal development has implications for bone mass in later life and that maternal fat stores in pregnancy are important for fetal bone mineral accrual. Objective: We investigated whether childhood bone mass is influenced by maternal body mass index (BMI) via an intrauterine mechanism by comparing parental associations. Design: We conducted a multivariable regression analysis of 7121 children from the Avon Longitudinal Study of Parents and Children. Total body less head (TBLH) and spine bone measures were derived from dual-energy X-ray absorptiometry scans at a mean age of 9.9 y. Maternal and paternal BMI values were derived from self-reported weight and height during pregnancy. Results: Maternal prepregnancy BMI (SD score) was positively associated with offspring TBLH bone mineral content and bone mineral density (SD scores) [mean difference (95% CI): boys, 0.19 (0.16, 0.23) and 0.15 (0.12, 0.19), respectively; girls, 0.23 (0.19, 0.26) and 0.19 (0.16, 0.23), respectively] and spine bone mineral content and bone mineral density [boys, 0.20 (0.16, 0.24) and 0.18 (0.14, 0.22), respectively; girls, 0.22 (0.18, 0.26) and 0.21 (0.17, 0.25), respectively] and with TBLH and spine bone area–and spine area–adjusted bone mineral content. Associations of paternal BMI with these outcomes were similar, with no statistical evidence of a difference between maternal and paternal effects. Maternal associations were partly explained by offspring birth weight and gestational age and attenuated to the null after adjustment for offspring height and weight. Conclusion: The positive relation between maternal prepregnancy BMI and offspring bone mass is likely due to shared familial, genetic, and environmental characteristics rather than to an intrauterine mechanism. Am J Clin Nutr 2010;92:872–80.

INTRODUCTION

Prenatal and early postnatal growth are important predictors of skeletal health in later life, with positive associations of birth weight and weight at 1 y found with bone mass at ages >60 y (1–4). The influence of the intrauterine environment on skeletal development has been further demonstrated by studies showing positive relations of maternal vitamin D status (5) and dietary micronutrient intake (6) during pregnancy with bone mineral accrual in offspring at age 9 y. Maternal triceps-fat stores in pregnancy have been shown to be positively related to bone mineral content (BMC) in neonates, which suggests that maternal fat stores are important for the skeletal development of the fetus (7, 8), but it is not known whether maternal adiposity during pregnancy is associated with bone mass later in childhood.

We assessed the associations of maternal prepregnancy body mass index (BMI) with skeletal size and bone density at a mean age of 9.9 y in a large cohort of children: the Avon Longitudinal Study of Parents and Children (ALSPAC). To investigate a potential intrauterine influence, we compared associations of maternal BMI with those of paternal BMI at a similar time, because maternal exposure would not be expected to influence the development of the fetus via an intrauterine mechanism. Hence, we would expect to see a stronger maternal association if the maternal exposure influenced childhood bone mass through a direct effect on fetal development, whereas similar sized maternal-paternal associations would suggest that relations were driven by shared familial, social, genetic, and environmental factors (9). This method was previously used to explore the relation of maternal prepregnancy BMI with offspring BMI in ALSPAC (10), and its validity is demonstrated by the incongruous associations of maternal and paternal smoking in pregnancy with offspring birth weight, which is known to be influenced by maternal smoking via an intrauterine mechanism (9).

SUBJECTS AND METHODS

ALSPAC

ALSPAC is a prospective birth cohort study that aims to investigate environmental and inheritable influences on the health

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and development of children. It was previously described in full elsewhere (11), and information can be found on the website www.alspac.bris.ac.uk. To be eligible for recruitment to the study, women had to be pregnant with expected delivery dates between 1 April 1991 and 31 December 1992 and living in a defined area of Avon, which included the city of Bristol and its surroundings. Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and from local ethics committees. A total of 14,541 women were enrolled in the study; of these, 13,678 had a singleton live birth. At age 9 y all children with known addresses who were still participating in the study were invited to a “Focus @ 9” clinic, and 7121 of the singleton children attended. Of these, 6868 underwent a full-body dual-energy X-ray absorptiometry (DXA) scan.

**DXA measurements**

Whole-body DXA scans were carried out by using a Lunar Prodigy scanner. After exclusion of those containing artifacts, movement, or skeletal irregularities, 6775 scans remained. The scans were reanalyzed to define borders between the main body regions, and measurements for total body less head (TBLH) BMC, bone area (BA), and areal BMD were calculated. A total of 122 pairs of scans were repeated on the same day, and the CV for TBLH BMD was 0.84%. Further reanalysis defined the spine subregion from the top of the thoracic spine to the top of the pelvis and laterally to the bone/soft tissue interface, and BMC, BA, and BMD were calculated for this subregion. Because curvature in the image of the spine leads to contamination of the spinal region with the ribs, the images were graded on a scale from A = perfect (no curvature) to D = suspected scoliosis, and only categories A and B (minor curvature) are used here in the analysis of spinal bone outcomes. For both TBLH and the spine subregion, area-adjusted BMC (ABMC) was derived as a measure of volumetric BMD by using linear regression to adjust BMC for BA. The residuals of these linear regressions were then added to the mean BMC for the region to give values for TBLH and spine ABMC. At the same time as the DXA scan, the child’s standing height (without shoes) was measured with a Harpenden Stadiometer (Holtain Ltd, Crosswell, United Kingdom), and weight (subjects unshod and in light clothing) was measured with a Tanita Body Fat Analyzer (Tanita UK Ltd, Viewsley, United Kingdom).

**Maternal and paternal BMI**

Maternal BMI was derived from height and prepregnancy weight measurements that were reported by the mother in a questionnaire administered during pregnancy. This weight measurement was found to correlate highly with the mother’s weight at the first antenatal visit (r = 0.95). Maternal prepregnancy BMI was also highly correlated with her postnatal (at 8 wk) BMI (r = 0.89), which suggested that maternal prepregnancy BMI is a good proxy for her BMI throughout pregnancy. Paternal BMI was obtained from height and weight measurements provided by the mother’s partner during pregnancy.

**Other variables**

Maternal and paternal highest educational qualifications, household social class, maternal smoking during pregnancy, father’s age, and mother’s parity were obtained from questionnaires administered during pregnancy. Household social class was defined from the highest parental occupation on a scale from I to V, with I indicating a professional/managerial role and V being unskilled manual. The child’s sex was obtained at the time of birth, and the child’s birth weight and gestational age and the mother’s age at delivery were abstracted from obstetric records.

Pubertal stage data for the children were obtained from Tanner stage questionnaires completed by the parents, which were available for 67% of the boys and 79% of the girls at age 9 y. For boys, Tanner stage assessment was based on pubic hair development, whereas for girls it was based on breast development or on pubic hair development if these data were missing. Most children (99% of boys and 96% of girls) for whom pubertal stage information was available were in Tanner stages 1 or 2, which indicated that they were prepubertal or early pubertal. For this reason, and because there was a large proportion of children with missing pubertal stage data, this was not adjusted for in the regression analysis.

**Paternity**

The child’s mother was asked in a questionnaire administered during pregnancy whether she believed her partner to be the child’s biological father. For partners for whom the mother had not answered “yes,” paternal information (BMI, age, height, and education) was treated as missing.

**Statistical analysis**

We assessed the associations of maternal and paternal BMI with offspring bone outcomes in separate regression models and also in combined models including both exposures to allow comparison of the strength of each association while adjusting for the exposure of the other parent. We adjusted initially for the child’s age and sex in model 1 and then additionally for the potential confounders of household social class, parity, paternal smoking during pregnancy, and maternal and paternal age, height, and education in model 2. Maternal factors were adjusted for in maternal exposure models, paternal factors were adjusted for in paternal exposure models, and both maternal and paternal factors were included in combined models. We assessed mediation by adjusting for the child’s birth weight and gestational age in model 3 and additionally for the child’s height and weight at age 9 y in model 4. The bone outcomes considered were TBLH and spine BMC, BA, BMD, and ABMC. The exposure variables of maternal and paternal BMI and the bone outcomes were each standardized to have a mean of 0 and an SD of 1, producing SD scores. The resulting regression coefficients are interpreted as the mean number of SD changes in the outcome variable associated with an increase of 1 SD in the exposure variable.

We used multivariate multiple imputation to account for missing data to reduce selection bias and increase efficiency. We included all children who attended the clinic at age 9 y in TBLH bone analysis but only children with none or minor curvature of the spinal image in spinal bone analysis. In this process, missing data were imputed by using switching regression (12) repeatedly to produce 10 full data sets each for the TBLH and spinal bone analyses. All exposures, outcomes, covariates, and predictors of missingness were included in prediction models to impute data.
except for TBLH and spine ABMC because these were derived from TBLH and spine BMC and BA. These variables were later rederived for each of the multiply imputed data sets. TBLH and spine BMD were passively imputed from BMC and BA at the corresponding regions, because BMD is equal to BMC/BA, and were not used in prediction models for these variables. For details of the variables used in prediction models, see Supplemental Table 1 under “Supplemental data” in the online issue. For the multiple regression analysis, model coefficients were averaged over the 10 data sets by using Rubin’s rules to produce SEs, which represented the uncertainty in the estimates due to the missing data (12). Because there was evidence of interactions of the child’s sex with maternal BMI, we imputed data separately for boys and girls and used sex-specific regression models and SD scores.

To consider the possible effect of nonpaternity in producing greater maternal associations compared with paternal associations due to the nonbiological relation between the child and the apparent father in some families, we used sensitivity analysis, using Steer’s correction to the Clemons’ method (13), for a range of possible nonpaternity rates between 1% and 10%. All analyses were carried out in Stata version 11.0.

RESULTS

The characteristics of the children who attended the 9-y clinic are given in Table 1. Children who attended the 9-y clinic had a slightly higher mean birth weight than did those who did not (mean difference: 0.07 kg, P < 0.001) and were more likely to be of a higher social class and have parents with higher educational qualifications (chi-square tests: all P < 0.001). No differences in maternal or paternal BMI were observed between children who attended the 9-y clinic and those who did not.

Maternal prepregnancy BMI was positively associated with the child’s birth weight and height and weight at age 9 y (see Supplemental Table 2 under “Supplemental data” in the online issue). Mothers with a higher BMI were more likely to be multiparous and were less likely to be of a nonmanual social class. For pairwise correlations of total body and spinal bone measures, see Supplemental Table 3 under “Supplemental data” in the online issue; correlations of these measures with child and parental characteristics are provided in Supplemental Table 4 under “Supplemental data” in the online issue. The child’s height and weight at age 9 y had strong positive correlations with TBLH and spine BMC and BA and moderate positive correlations with TBLH and spine BMD. Higher birth weight, longer gestation, and older age at the time of the DXA scan were all associated with increased TBLH BMC, BA, and BMD at age 9 y. Birth weight and age at the time of the DXA scan were also positively associated with spinal BMC, BA, and BMD.

In both boys and girls, very strong positive associations were observed between maternal prepregnancy BMI and TBLH BMC, BA, and BMD and spinal BMC, BA, BMD, and ABMC in confounder-adjusted models (Tables 2 and 3). These associations were attenuated little, if at all, by adjustment for the child’s birth weight and gestational age. Generally, these associations were larger in girls than in boys (P values for sex differences = 0.009, 0.011, and 0.025 for TBLH BMC, BA, and BMD, respectively, and 0.044, 0.298, 0.016, and 0.025 for spine BMC, BA, BMD, and ABMC). Associations between paternal BMI

| Characteristic | No. with data (%) | Value |
|---------------|------------------|-------|
| Child         |                  |       |
| Age at DXA scan (mo) | 6851 (96.2) | 118.4 ± 3.9
| Sex (%)       | Male 7121 (100.0) | 49.6 |
|               | Female 50.4      | 50.4  |
| Height (cm)   | 7047 (99.0)      | 139.5 ± 6.3 |
| Weight (kg)   | 7105 (99.8)      | 33.2 (29.4, 38.4) |
| TBLH BMC (g)  | 6775 (95.1)      | 893.8 ± 184.0 |
| TBLH BA (cm²) | 6775 (95.1)      | 1139.5 ± 164.3 |
| TBLH BMD (g/cm²) | 6775 (95.1) | 0.78 ± 0.05 |
| TBLH ABMC (g) | 6775 (95.1)      | 894.6 ± 39.8 |
| Spine BMC (g) | 5487 (77.1)      | 78.4 ± 15.7 |
| Spine BA (cm²) | 5487 (77.1) | 100.7 ± 12.0 |
| Spine BMD (g/cm²) | 5487 (77.1) | 0.77 ± 0.08 |
| Spine ABMC (g) | 5487 (77.1) | 78.4 ± 7.1 |
| Pubertal stage (%) |            |       |
| Boys          | Tanner 1 2365 (67.0) | 82.9 |
|               | Tanner 2 16.5 |
|               | Tanner ≥3 0.6 |
| Girls         | Tanner 1 2836 (79.0) | 81.5 |
|               | Tanner 2 15.0 |
|               | Tanner ≥3 3.5 |
| Gestational age (wk) | 7121 (100.0) | 39.5 ± 1.8 |
| Birth weight (kg) | 7035 (98.8) | 3.4 ± 0.5 |
| Household social class (%) | 6544 (91.9) | 15.5 |
| I             | 6544 (91.9) | 15.5 |
| II            | 45.1 |
| III NM        | 24.8 |
| III M         | 10.3 |
| IV/N          | 4.3 |
| Mother        | Age at delivery (y) | 7121 (100.0) | 29.0 ± 4.6 |
|               | Height (cm) 6753 (94.8) | 164.1 ± 6.6 |
| Prepregnancy BMI (kg/m²) | 6429 (90.3) | 22.2 (20.5, 24.4) |
| Number of previous births (%) | 6879 (96.6) | 45.8 |
| 0             | 45.8 |
| 1             | 35.5 |
| 2             | 13.7 |
| 3             | 3.8 |
| ≥4            | 1.2 |
| Smoking during pregnancy (%) | 6379 (89.6) | 78.7 |
| Never         | 78.7 |
| 1 or 2 trimesters | 9.5 |
| All trimesters | 11.8 |
| Education (%) | None/CSE 6860 (96.3) | 13.8 |
|               | Vocational 8.5 |
|               | O levels 35.2 |
|               | A levels 26.6 |
|               | Degree 15.8 |
| Father        | Age at child’s birth (y) | 5106 (71.7) | 31.4 ± 5.2 |
|               | Height (cm) 4931 (69.2) | 176.3 ± 6.9 |
| BMI (kg/m²)   | 4887 (88.6) | 24.8 (22.9, 26.9) |
| Education (%) | None/CSE 6467 (90.8) | 19.3 |
|               | Vocational 8.2 |
|               | O levels 21.7 |
|               | A levels 28.5 |
|               | Degree 22.2 |

* BMC, bone mineral content; BMD, bone mineral density; NM, nonmanual; M, manual; CSE, Certificate of Secondary Education; DXA, dual-energy X-ray absorptiometry; ABMC, area-adjusted BMC; BA, bone area; TBLH, total body less head; O levels, educational qualifications acquired at school at age 16 y; A levels, educational qualifications generally acquired at school at age 18 y.

** Mean ± SD (all such values).

*** Median; interquartile range in parentheses (for skewed variables).
TABLE 2
Sex-specific associations of maternal and paternal BMIs with total body less head (TBLH) bone outcomes at age 9 y in multiple imputation analyses

|                  | Boys (n = 3530) |        |       |        |         | Girls (n = 3591) |        |       |        |         |
|------------------|-----------------|--------|-------|--------|---------|-----------------|--------|-------|--------|---------|
|                  | Mean difference | 95% CI | P value | Mean difference | 95% CI | P value | Mean difference | 95% CI | P value | Mean difference | 95% CI | P value |
| **TBLH BMC (SD score)** |                 |        |        |        |         |                 |        |        |        |         |                 |        |        |        |         |
| Maternal prepregnancy BMI (SD score) |                 |        |        |        |         |                 |        |        |        |         |                 |        |        |        |         |
| Model 1          | 0.15 (0.12, 0.19) | <0.001 |        | 0.19 (0.16, 0.23) | <0.001 |        | 0.01 (0.16, 0.19) | <0.001 |        |        |         |                 |        |        |        |         |
| Model 2          | 0.19 (0.16, 0.23) | <0.001 |        | 0.23 (0.19, 0.26) | <0.001 |        | 0.01 (0.16, 0.20) | <0.001 |        |        |         |                 |        |        |        |         |
| Model 3          | 0.16 (0.13, 0.20) | <0.001 |        | 0.20 (0.17, 0.24) | <0.001 |        | 0.01 (0.13, 0.19) | <0.001 |        |        |         |                 |        |        |        |         |
| Model 4          | 0.00 (−0.01, 0.02) | 0.644 | 0.01 | 0.00 (−0.01, 0.04) | 0.377 | 0.02 | (−0.00, 0.04) | 0.053 |        |        |         |                 |        |        |        |         |
| Paternal BMI (SD score) |                 |        |        |        |         |                 |        |        |        |         |                 |        |        |        |         |
| Model 1          | 0.21 (0.16, 0.25) | <0.001 |        | 0.18 (0.14, 0.22) | <0.001 |        | 0.01 (−0.02, 0.02) | 0.840 | 0.01 | (−0.01, 0.02) | 0.322 |        |        |         |         |
| Model 2          | 0.22 (0.18, 0.26) | <0.001 |        | 0.20 (0.16, 0.23) | <0.001 |        | 0.01 (−0.01, 0.04) | 0.342 | 0.02 | (−0.00, 0.04) | 0.056 |        |        |         |         |
| Combined models (SD score) |                 |        |        |        |         |                 |        |        |        |         |                 |        |        |        |         |
| Model 1          | 0.12 (0.09, 0.16) | <0.001 |        | 0.17 (0.14, 0.20) | <0.001 |        | 0.00 (−0.02, 0.02) | 0.548 | 0.01 | (−0.00, 0.02) | 0.147 |        |        |         |         |
| Model 2          | 0.17 (0.14, 0.20) | <0.001 |        | 0.19 (0.16, 0.23) | <0.001 |        | 0.01 (−0.00, 0.03) | 0.137 | 0.02 | (0.00, 0.04) | 0.046 |        |        |         |         |
| Model 3          | 0.18 (0.14, 0.22) | <0.001 |        | 0.16 (0.12, 0.19) | <0.001 |        | 0.01 (−0.01, 0.02) | 0.735 | 0.01 | (−0.01, 0.02) | 0.291 |        |        |         |         |
| Model 4          | 0.00 (−0.01, 0.02) | 0.120 | 0.02 | (−0.00, 0.04) | 0.120 | 0.02 | (0.00, 0.04) | 0.043 |        |        |         |                 |        |        |        |         |
| **TBLH BA (SD score)** |                 |        |        |        |         |                 |        |        |        |         |                 |        |        |        |         |
| Maternal prepregnancy BMI (SD score) |                 |        |        |        |         |                 |        |        |        |         |                 |        |        |        |         |
| Model 1          | 0.15 (0.12, 0.19) | <0.001 |        | 0.19 (0.16, 0.22) | <0.001 |        | 0.01 (0.16, 0.20) | <0.001 |        |        |         |                 |        |        |        |         |
| Model 2          | 0.20 (0.17, 0.23) | <0.001 |        | 0.22 (0.19, 0.25) | <0.001 |        | 0.01 (0.16, 0.23) | <0.001 |        |        |         |                 |        |        |        |         |
| Model 3          | 0.16 (0.13, 0.20) | <0.001 |        | 0.20 (0.17, 0.23) | <0.001 |        | 0.01 (0.17, 0.21) | <0.001 |        |        |         |                 |        |        |        |         |
| Model 4          | 0.00 (−0.01, 0.02) | 0.548 | 0.01 | (−0.00, 0.02) | 0.137 | 0.02 | (0.00, 0.04) | 0.046 |        |        |         |                 |        |        |        |         |
| Paternal BMI (SD score) |                 |        |        |        |         |                 |        |        |        |         |                 |        |        |        |         |
| Model 1          | 0.17 (0.14, 0.20) | <0.001 |        | 0.19 (0.16, 0.23) | <0.001 |        | 0.01 (0.16, 0.20) | <0.001 |        |        |         |                 |        |        |        |         |
| Model 2          | 0.19 (0.15, 0.23) | <0.001 |        | 0.16 (0.12, 0.19) | <0.001 |        | 0.01 (0.15, 0.21) | <0.001 |        |        |         |                 |        |        |        |         |
| Model 3          | 0.18 (0.15, 0.22) | <0.001 |        | 0.15 (0.11, 0.19) | <0.001 |        | 0.01 (0.11, 0.19) | <0.001 |        |        |         |                 |        |        |        |         |
| Model 4          | 0.00 (−0.01, 0.02) | 0.735 | 0.01 | (−0.01, 0.02) | 0.735 | 0.01 | (−0.00, 0.02) | 0.291 |        |        |         |                 |        |        |        |         |
| Combined models (SD score) |                 |        |        |        |         |                 |        |        |        |         |                 |        |        |        |         |
| Model 1          | 0.12 (0.09, 0.16) | <0.001 |        | 0.16 (0.13, 0.20) | <0.001 |        | 0.00 (−0.02, 0.03) | 0.679 | 0.01 | (−0.01, 0.04) | 0.317 |        |        |         |         |
| Model 2          | 0.15 (0.12, 0.19) | <0.001 |        | 0.19 (0.16, 0.23) | <0.001 |        | 0.01 (−0.02, 0.03) | 0.690 | 0.03 | (−0.00, 0.05) | 0.055 |        |        |         |         |

(Continued)
and these outcomes were of a similar size to maternal associations, and $P$ values for differences between maternal and paternal effects were all $>$0.2 in combined confounder-adjusted models. There was a tendency for maternal relationships to be marginally larger than paternal relationships in girls, especially in models with spinal bone outcomes; however, these differences were never $>$0.04 SD and decreased in size when we adjusted for potential rates of nonpaternity (see Supplemental Tables 5 and 6 under “Supplemental data” in the online issue).

In boys, paternal associations were generally slightly larger than maternal associations in confounder-adjusted models, and these differences increased when corrected for nonpaternity (see Supplemental Tables 5 and 6 under “Supplemental data” in the online issue). Although paternal associations tended to be larger in boys than in girls, all $P$ values for sex differences were $>$0.15. Neither maternal nor paternal BMI was associated with TBLH ABMC. After adjustment for the child’s height and weight at age 9 y, there remained no associations of maternal BMI with TBLH or spinal bone outcomes, although weak associations remained between paternal BMI and TBLH and spine BMC, BA, and BMD in girls but not in boys. Adjustment for offspring BMI in place of height and weight led to similarly attenuated coefficients (results available from authors on request), which suggests that it is offspring adiposity that is driving these associations.

The results of the complete case analysis (ie, without multiple imputation) were similar in boys, but showed greater maternal associations and smaller paternal associations with TBLH and

| TABLE 2 (Continued) |
|----------------------|
| Boys ($n = 3530$) | Girls ($n = 3591$) |
| Mean difference | 95% CI | $P$ value | Mean difference | 95% CI | $P$ value |
| Combined models (SD scores) | | | | | |
| Model 1 | | | | | |
| Maternal BMI | 0.10 | (0.07, 0.14) | $<$0.001 | 0.15 | (0.11, 0.18) | $<$0.001 |
| Paternal BMI | 0.14 | (0.10, 0.19) | $<$0.001 | 0.14 | (0.10, 0.17) | $<$0.001 |
| Model 2 | | | | | |
| Maternal BMI | 0.13 | (0.10, 0.17) | $<$0.001 | 0.17 | (0.13, 0.20) | $<$0.001 |
| Paternal BMI | 0.14 | (0.09, 0.19) | $<$0.001 | 0.14 | (0.11, 0.18) | $<$0.001 |
| Model 3 | | | | | |
| Maternal BMI | 0.12 | (0.08, 0.15) | $<$0.001 | 0.16 | (0.12, 0.19) | $<$0.001 |
| Paternal BMI | 0.14 | (0.09, 0.19) | $<$0.001 | 0.14 | (0.10, 0.18) | $<$0.001 |
| Model 4 | | | | | |
| Maternal BMI | 0.00 | (–0.03, 0.03) | 0.820 | 0.01 | (–0.01, 0.04) | 0.349 |
| Paternal BMI | 0.01 | (–0.03, 0.05) | 0.646 | 0.03 | (–0.00, 0.05) | 0.073 |
| TBLH ABMC (SD score) | | | | | |
| Maternal prepregnancy BMI (SD score) | | | | | |
| Model 1 | 0.02 | (–0.01, 0.06) | 0.239 | 0.04 | (0.00, 0.07) | 0.041 |
| Model 2 | 0.01 | (–0.03, 0.05) | 0.561 | 0.03 | (–0.01, 0.06) | 0.171 |
| Model 3 | 0.02 | (–0.01, 0.06) | 0.216 | 0.04 | (0.00, 0.08) | 0.039 |
| Model 4 | 0.00 | (–0.04, 0.04) | 0.941 | 0.00 | (–0.04, 0.04) | 0.979 |
| Paternal BMI (SD score) | | | | | |
| Model 1 | 0.00 | (–0.04, 0.05) | 0.900 | 0.03 | (–0.01, 0.06) | 0.191 |
| Model 2 | 0.01 | (–0.06, 0.04) | 0.681 | 0.02 | (–0.02, 0.06) | 0.338 |
| Model 3 | 0.00 | (–0.05, 0.04) | 0.899 | 0.02 | (–0.01, 0.06) | 0.213 |
| Model 4 | 0.01 | (–0.06, 0.04) | 0.591 | 0.00 | (–0.04, 0.04) | 0.924 |
| Combined models (SD scores) | | | | | |
| Model 1 | | | | | |
| Maternal BMI | 0.02 | (–0.02, 0.06) | 0.266 | 0.03 | (–0.00, 0.07) | 0.073 |
| Paternal BMI | 0.00 | (–0.05, 0.05) | 0.994 | 0.02 | (–0.02, 0.06) | 0.340 |
| Model 2 | | | | | |
| Maternal BMI | 0.01 | (–0.03, 0.05) | 0.640 | 0.03 | (–0.01, 0.07) | 0.132 |
| Paternal BMI | 0.00 | (–0.05, 0.04) | 0.848 | 0.02 | (–0.02, 0.06) | 0.414 |
| Model 3 | | | | | |
| Maternal BMI | 0.02 | (–0.02, 0.06) | 0.328 | 0.04 | (0.00, 0.08) | 0.039 |
| Paternal BMI | 0.00 | (–0.05, 0.05) | 0.964 | 0.02 | (–0.02, 0.06) | 0.352 |
| Model 4 | | | | | |
| Maternal BMI | 0.00 | (–0.04, 0.04) | 0.876 | 0.00 | (–0.03, 0.04) | 0.809 |
| Paternal BMI | 0.01 | (–0.06, 0.04) | 0.636 | 0.00 | (–0.04, 0.04) | 0.970 |

$^2$ BMC, bone mineral content; BMD, bone mineral density; ABMC, area-adjusted BMC; BA, bone area. Multiple regression models: model 1 was adjusted for the child’s age; model 2 was adjusted for the child’s age, mother’s parity, maternal smoking during pregnancy, household social class, and maternal and paternal factors (age, height, and education); model 3 was further adjusted for birth weight and gestational age; and model 4 was further adjusted for the child’s height and weight at age 9 y. Sex-specific SDs for boys and girls, respectively, were as follows: TBLH BMC, 174.6 and 191.5 g; TBLH BA, 154.9 and 172.3 cm²; TBLH BMD, 0.053 and 0.055 g/cm²; TBLH ABMC, 40.3 and 39.3 g; maternal BMI (in kg/m²), 3.8 and 3.7; paternal BMI, 3.2 and 3.4.
### TABLE 3
Sex-specific associations of maternal and paternal BMIs with spinal bone outcomes at age 9 y in multiple imputation analyses

|                | Boys (n = 2772)          |         |         |          | Girls (n = 2715)          |         |         |          |
|----------------|-------------------------|---------|---------|----------|-------------------------|---------|---------|----------|
|                | Mean difference | 95% CI   | P value |          | Mean difference | 95% CI   | P value |          |
| Spine BMC (SD score) |                         |         |         |          |                         |         |         |          |
| Maternal prepregnancy BMI (SD score) |                     |         |         |          |                         |         |         |          |
| Model 1        | 0.16                    | (0.13, 0.20) | <0.001 |          | 0.19                    | (0.15, 0.23) | <0.001 |          |
| Model 2        | 0.20                    | (0.16, 0.24) | <0.001 |          | 0.22                    | (0.18, 0.26) | <0.001 |          |
| Model 3        | 0.18                    | (0.14, 0.22) | <0.001 |          | 0.20                    | (0.16, 0.24) | <0.001 |          |
| Model 4        | 0.01                    | (~0.02, 0.03) | 0.655 |          | 0.01                    | (~0.01, 0.04) | 0.279 |          |
| Paternal BMI (SD score) |                     |         |         |          |                         |         |         |          |
| Model 1        | 0.20                    | (0.16, 0.24) | <0.001 |          | 0.18                    | (0.13, 0.22) | <0.001 |          |
| Model 2        | 0.22                    | (0.18, 0.27) | <0.001 |          | 0.19                    | (0.15, 0.24) | <0.001 |          |
| Model 3        | 0.21                    | (0.16, 0.25) | <0.001 |          | 0.18                    | (0.14, 0.22) | <0.001 |          |
| Model 4        | 0.02                    | (~0.01, 0.05) | 0.200 |          | 0.03                    | (0.01, 0.06) | 0.014 |          |
| Combined models (SD scores) |                 |         |         |          |                         |         |         |          |
| Model 1        | 0.14                    | (0.10, 0.18) | <0.001 |          | 0.17                    | (0.13, 0.20) | <0.001 |          |
| Model 2        | 0.18                    | (0.14, 0.22) | <0.001 |          | 0.15                    | (0.10, 0.19) | <0.001 |          |
| Model 3        | 0.18                    | (0.14, 0.22) | <0.001 |          | 0.19                    | (0.15, 0.23) | <0.001 |          |
| Model 4        | 0.00                    | (~0.02, 0.03) | 0.716 |          | 0.01                    | (~0.01, 0.03) | 0.386 |          |
| Spine BA (SD score) |                         |         |         |          |                         |         |         |          |
| Maternal prepregnancy BMI (SD score) |                     |         |         |          |                         |         |         |          |
| Model 1        | 0.13                    | (0.10, 0.17) | <0.001 |          | 0.15                    | (0.11, 0.19) | <0.001 |          |
| Model 2        | 0.17                    | (0.14, 0.21) | <0.001 |          | 0.19                    | (0.15, 0.22) | <0.001 |          |
| Model 3        | 0.14                    | (0.11, 0.18) | <0.001 |          | 0.16                    | (0.12, 0.20) | <0.001 |          |
| Model 4        | 0.00                    | (~0.02, 0.03) | 0.882 |          | 0.01                    | (~0.01, 0.03) | 0.485 |          |
| Paternal BMI (SD score) |                     |         |         |          |                         |         |         |          |
| Model 1        | 0.17                    | (0.13, 0.21) | <0.001 |          | 0.15                    | (0.10, 0.20) | <0.001 |          |
| Model 2        | 0.20                    | (0.16, 0.24) | <0.001 |          | 0.17                    | (0.12, 0.22) | <0.001 |          |
| Model 3        | 0.18                    | (0.14, 0.22) | <0.001 |          | 0.16                    | (0.11, 0.20) | <0.001 |          |
| Model 4        | 0.01                    | (~0.02, 0.04) | 0.589 |          | 0.03                    | (~0.00, 0.06) | 0.064 |          |
| Combined models (SD scores) |                 |         |         |          |                         |         |         |          |
| Model 1        | 0.11                    | (0.07, 0.15) | <0.001 |          | 0.13                    | (0.09, 0.17) | <0.001 |          |
| Model 2        | 0.15                    | (0.11, 0.20) | <0.001 |          | 0.13                    | (0.08, 0.18) | <0.001 |          |
| Model 3        | 0.16                    | (0.12, 0.19) | <0.001 |          | 0.16                    | (0.12, 0.19) | <0.001 |          |
| Model 4        | 0.15                    | (0.11, 0.19) | <0.001 |          | 0.13                    | (0.09, 0.18) | <0.001 |          |
| Paternal BMI (SD score) |                     |         |         |          |                         |         |         |          |
| Model 1        | 0.13                    | (0.10, 0.17) | <0.001 |          | 0.14                    | (0.10, 0.18) | <0.001 |          |
| Model 2        | 0.16                    | (0.12, 0.20) | <0.001 |          | 0.13                    | (0.09, 0.18) | <0.001 |          |
| Model 3        | 0.00                    | (~0.02, 0.03) | 0.827 |          | 0.01                    | (~0.02, 0.03) | 0.641 |          |
| Model 4        | 0.01                    | (~0.02, 0.04) | 0.588 |          | 0.03                    | (~0.00, 0.06) | 0.088 |          |
| Spine BMD (SD score) |                         |         |         |          |                         |         |         |          |
| Maternal prepregnancy BMI (SD score) |                     |         |         |          |                         |         |         |          |
| Model 1        | 0.15                    | (0.11, 0.19) | <0.001 |          | 0.19                    | (0.15, 0.23) | <0.001 |          |
| Model 2        | 0.18                    | (0.14, 0.22) | <0.001 |          | 0.21                    | (0.17, 0.25) | <0.001 |          |
| Model 3        | 0.16                    | (0.12, 0.20) | <0.001 |          | 0.20                    | (0.16, 0.24) | <0.001 |          |
| Model 4        | 0.01                    | (~0.02, 0.04) | 0.581 |          | 0.02                    | (~0.02, 0.05) | 0.318 |          |
| Paternal BMI (SD score) |                     |         |         |          |                         |         |         |          |
| Model 1        | 0.18                    | (0.14, 0.23) | <0.001 |          | 0.17                    | (0.13, 0.21) | <0.001 |          |
| Model 2        | 0.19                    | (0.15, 0.24) | <0.001 |          | 0.18                    | (0.13, 0.22) | <0.001 |          |
| Model 3        | 0.18                    | (0.14, 0.23) | <0.001 |          | 0.17                    | (0.13, 0.21) | <0.001 |          |
| Model 4        | 0.03                    | (~0.01, 0.08) | 0.110 |          | 0.03                    | (~0.00, 0.07) | 0.077 |          |

(Continued)
spinal bone outcomes in girls (see Supplemental Tables 7 and 8 under "Supplemental data" in the online issue), with some evidence of a stronger maternal effect. There was also statistical evidence for remaining associations of maternal BMI with TBLH BMC and BA and spine BMC in girls after adjustment for the child’s size at age 9 y in the complete case, which were not evident in the multiply imputed data. See Supplemental Tables 9 and 10 under “Supplemental data” in the online issue for comparisons of the distributions of child and parent characteristics in the complete case and multiply imputed data sets. In the complete case, a smaller proportion of parents was educated to lower qualification levels compared with the multiply imputed data sets and also compared with the observed data (Table 1). We stratified the complete case into categories, for which neither one or both parents had an A level or a higher qualification and investigated univariate relations of maternal and paternal BMI with TBLH and spinal bone outcomes in each stratum. In the stratum in which neither parents had an A level or higher qualification, there was either a smaller maternal association or a greater paternal association with each of the bone outcomes than in the other strata, which led to a smaller difference between maternal and paternal effects. This suggests that the differences in the complete case analysis are explained by selection bias because of missing data for less-educated families.

Restricting the analysis to only children of white ethnicity or to only prepubertal and early-pubertal children (Tanner Stages 1 and 2) did not meaningfully change the model coefficients compared with the complete case analyses for any of the bone outcomes studied.

| Boys (n = 2772) | Mean difference | 95% CI | P value | Girls (n = 2715) | Mean difference | 95% CI | P value |
|----------------|----------------|--------|--------|----------------|----------------|--------|--------|
| Combined models (SD scores) | | | | | | | |
| Model 1 | | | | | | | |
| Maternal BMI | 0.13 | (0.09, 0.16) | <0.001 | 0.17 | (0.13, 0.21) | <0.001 | |
| Paternal BMI | 0.16 | (0.12, 0.21) | <0.001 | 0.14 | (0.10, 0.18) | <0.001 | |
| Model 2 | | | | | | | |
| Maternal BMI | 0.15 | (0.11, 0.19) | <0.001 | 0.18 | (0.14, 0.22) | <0.001 | |
| Paternal BMI | 0.16 | (0.12, 0.21) | <0.001 | 0.14 | (0.10, 0.18) | <0.001 | |
| Model 3 | | | | | | | |
| Maternal BMI | 0.14 | (0.10, 0.18) | <0.001 | 0.17 | (0.13, 0.22) | <0.001 | |
| Paternal BMI | 0.16 | (0.12, 0.20) | <0.001 | 0.14 | (0.10, 0.18) | <0.001 | |
| Model 4 | | | | | | | |
| Maternal BMI | 0.01 (−0.03, 0.04) | 0.719 | | 0.01 (−0.02, 0.05) | 0.390 | | |
| Paternal BMI | 0.03 (−0.01, 0.08) | 0.109 | | 0.03 (−0.01, 0.07) | 0.105 | | |

Spine ABMC (SD score)

| Boys (n = 2772) | Mean difference | 95% CI | P value | Girls (n = 2715) | Mean difference | 95% CI | P value |
|----------------|----------------|--------|--------|----------------|----------------|--------|--------|
| Combined models (SD scores) | | | | | | | |
| Maternal prepregnancy BMI (SD score) | | | | | | | |
| Model 1 | | | | | | | |
| Maternal BMI | 0.09 | (0.05, 0.13) | <0.001 | 0.14 | (0.10, 0.18) | <0.001 | |
| Paternal BMI | 0.09 | (0.05, 0.13) | <0.001 | 0.14 | (0.10, 0.18) | <0.001 | |
| Model 2 | | | | | | | |
| Maternal BMI | 0.10 | (0.06, 0.14) | <0.001 | 0.15 | (0.10, 0.19) | <0.001 | |
| Paternal BMI | 0.10 | (0.06, 0.14) | <0.001 | 0.10 | (0.06, 0.15) | <0.001 | |
| Model 3 | | | | | | | |
| Maternal BMI | 0.01 (−0.03, 0.05) | 0.675 | | 0.01 (−0.03, 0.06) | 0.510 | | |
| Paternal BMI | 0.09 | (0.04, 0.13) | <0.001 | 0.10 | (0.06, 0.15) | <0.001 | |
| Model 4 | | | | | | | |
| Maternal BMI | 0.10 | (0.05, 0.14) | <0.001 | 0.11 | (0.06, 0.16) | <0.001 | |
| Paternal BMI | 0.09 | (0.04, 0.13) | <0.001 | 0.10 | (0.06, 0.15) | <0.001 | |
| Model 3 | | | | | | | |
| Maternal BMI | 0.10 | (0.05, 0.14) | <0.001 | 0.11 | (0.06, 0.15) | <0.001 | |
| Paternal BMI | 0.09 | (0.04, 0.13) | <0.001 | 0.10 | (0.06, 0.15) | <0.001 | |
| Model 4 | | | | | | | |
| Maternal BMI | 0.03 (−0.02, 0.08) | 0.211 | | 0.01 (−0.04, 0.06) | 0.554 | | |
| Paternal BMI | 0.08 | (0.04, 0.12) | <0.001 | 0.13 | (0.09, 0.17) | <0.001 | |
| Model 2 | | | | | | | |
| Maternal BMI | 0.08 (0.03, 0.13) | 0.001 | | 0.09 (0.04, 0.13) | <0.001 | | |
| Paternal BMI | 0.08 | (0.04, 0.12) | <0.001 | 0.13 | (0.08, 0.17) | <0.001 | |
| Model 3 | | | | | | | |
| Maternal BMI | 0.08 | (0.04, 0.13) | <0.001 | 0.09 (0.04, 0.13) | 0.001 | | |
| Paternal BMI | 0.08 | (0.04, 0.12) | <0.001 | 0.13 | (0.09, 0.17) | <0.001 | |
| Model 4 | | | | | | | |
| Maternal BMI | 0.00 (−0.04, 0.05) | 0.827 | | 0.01 (−0.03, 0.06) | 0.527 | | |
| Paternal BMI | 0.03 (−0.02, 0.08) | 0.217 | | 0.01 (−0.04, 0.06) | 0.598 | | |

1 BMC, bone mineral content; BMD, bone mineral density; ABMC, area-adjusted BMC; BA, bone area. Multiple regression models: model 1 was adjusted for the child’s age; model 2 was adjusted for the child’s age, mother’s parity, maternal smoking during pregnancy, household social class, and maternal and paternal factors (age, height, and education); model 3 was further adjusted for birth weight and gestational age; and model 4 was further adjusted for the child’s height and weight at age 9 y. Sex-specific SDs for boys and girls, respectively, were as follows: spine BMC, 14.8 and 16.7 g; spine BA, 11.7 and 12.3 cm²; spine BMD, 0.076 and 0.086 g/cm²; spine ABMC, 6.8 and 7.2 g; maternal BMI (in kg/m²), 3.8 and 3.8; paternal BMI, 3.2 and 3.4.

spinal bone outcomes in girls (see Supplemental Tables 7 and 8 under “Supplemental data” in the online issue), with some evidence of a stronger maternal effect. There was also statistical evidence for remaining associations of maternal BMI with TBLH BMC and BA and spine BMC in girls after adjustment for the child’s size at age 9 y in the complete case, which were not evident in the multiply imputed data. See Supplemental Tables 9 and 10 under “Supplemental data” in the online issue for comparisons of the distributions of child and parent characteristics in the complete case and multiply imputed data sets. In the complete case, a smaller proportion of parents was educated to lower qualification levels compared with the multiply imputed data sets and also compared with the observed data (Table 1). We stratified the complete case into categories, for which neither one or both parents had an A level or a higher qualification and investigated univariate relations of maternal and paternal BMI with TBLH and spinal bone outcomes in each stratum. In the stratum in which neither parents had an A level or higher qualification, there was either a smaller maternal association or a greater paternal association with each of the bone outcomes than in the other strata, which led to a smaller difference between maternal and paternal effects. This suggests that the differences in the complete case analysis are explained by selection bias because of missing data for less-educated families.

Restricting the analysis to only children of white ethnicity or to only prepubertal and early-pubertal children (Tanner Stages 1 and 2) did not meaningfully change the model coefficients compared with the complete case analyses for any of the bone outcomes studied.
DISCUSSION

We compared the relations of maternal prepregnancy BMI and paternal BMI with offspring bone mass in a large birth cohort and found both to be associated with increased total-body and spinal BMC, BA, and areal BMD and spinal ABMC in the offspring at a mean age of 9.9 y.

No evidence of an intrauterine effect of maternal prepregnancy BMI was observed, because maternal and paternal associations were of a similar size. Although maternal associations were slightly greater than paternal associations with female offspring bone mass, these differences were largely explained by the effect of unknown nonpaternity in the data because adjustment for plausible nonpaternity rates reduced the differences. Also, it is unlikely that these differences would be due to an intrauterine effect because any intrauterine mechanism would be expected to influence both sons and daughters. It is more likely due to social characteristics within families, for example, through daughters spending more time with their mothers than their fathers and therefore being more influenced by the mother’s lifestyle.

The relation between maternal prepregnancy BMI and offspring bone mass was explained partly by the child’s birth weight and gestational age, but mainly by offspring height and weight at age 9 y. The only relations that remained after adjustment for the child’s height and weight at age 9 y were between paternal BMI and bone outcomes in female offspring. These associations were small in magnitude, however, and generally were only supported by weak statistical evidence. On further investigation, we found that the relations of parental BMI with offspring bone mass were largely explained by the child’s BMI at the time of the DXA scan.

Although women may gain different amounts of adiposity during pregnancy, the high correlation between maternal prepregnancy BMI and postnatal BMI suggests that women who are more adipose at the beginning of pregnancy continue to be more adipose throughout pregnancy, on average. This indicates that prepregnancy BMI is a good indicator of fat stores throughout pregnancy. Studies have consistently shown a positive relation between maternal BMI and offspring BMI during childhood (10, 14–18). This could be partly due to the fetal overnutrition hypothesis, whereby offspring appetite, energy metabolism, and neuroendocrine function are programmed prenatally by the placental transfer of nutrients (19, 20), because mothers with high BMIs have increased plasma concentrations of glucose and fatty acids. However, studies comparing associations of maternal and paternal BMI with offspring BMI during childhood have been inconsistent in European-origin cohorts (10, 17, 18). The similar-sized associations that we found between maternal and paternal BMI and bone outcomes in the offspring suggest that bone mass in childhood is not influenced by fetal overnutrition but by genetic and postnatal environmental characteristics.

In our previous study in ALSPAC, we found that 2 of the principle determinants of BMI, namely total body lean mass and fat mass, are both strongly related to overall bone size and hence bone mass (21). Therefore, a positive relation between parental and child BMI is expected to result in an equivalent association between parental BMI and bone size and mass of the child. Because BMD is also size-dependent, because this term is incompletely adjusted for BA, a positive relation between parental BMI and bone size of the child would also explain the association we observed between parental BMI and child BMD. On the other hand, our observation that parental BMI is related to child ABMC via a pathway involving child BMI provides evidence that, as well as affecting bone size, determinants of BMI such as fat and lean mass also affect volumetric BMC, because, unlike BMD, ABMC is independent of skeletal size.

Theoretically, ABMC is likely to be influenced by 3 distinct bone characteristics that are independent of overall skeletal size, namely cortical thickness, cortical density, and trabecular bone volume. Because the observed association between parental BMI and child ABMC was restricted to the spine subregion, which has a relatively high proportion of trabecular bone, it seems likely that an influence on the amount of trabecular bone underlies this relation. This conclusion is consistent with results of a previous study based on the Gothenburg Osteoporosis and Obesity Determinants cohort of 1068 men aged 18 y, in whom total body lean mass, and to a lesser extent fat mass, was positively related to the extent of trabecular bone as reflected by trabecular volumetric BMD of the radius and tibia measured by peripheral quantitative computed tomography (22).

Whereas there was evidence of a greater maternal BMI-offspring bone mass relation compared with that of paternal BMI in the complete case analysis, the complete case had considerably different distributions of parental education levels, and further exploration suggested that these analyses might be influenced by selection bias because of a greater level of missing data in children of less-educated parents. Children of parents with low educational qualifications were less likely to attend the 9-y clinic than were children with more educated parents, which meant that it is also possible that, in the study population as a whole, maternal associations would be slightly smaller and paternal associations would be slightly greater than we found in the clinic attendees. Nevertheless, it seems probable that the multiple imputation analysis is more representative of the true relations in the study population than is the complete case analysis.

Our study was limited by the self-reported parental height and weight measurements. However self-reported height and weight, and derived BMI, were shown to correlate highly with measured values in both men and women in a middle-aged British population (23); in our cohort, maternal self-report of prepregnancy weight correlated highly with their actual measured weight at their first antenatal clinic visit. We did not adjust for puberty in the analysis because of a large proportion of missing pubertal stage data, but the vast majority of children were prepubertal or early pubertal, and we found that restricting the analysis to only prepubertal or early-pubertal children made no substantial changes to the findings. Furthermore, pubertal stage of the child at age 9–10 y could not influence parental BMI at the time of pregnancy; therefore, puberty could not confound the associations that we explored. Our study benefitted from its large size and its ability to control for a number of potential confounders, including 2 markers of social position: household social class and parental education level and also the ability to compare associations of bone outcomes with both maternal and paternal exposures to assess the level of residual confounding.

In conclusion, we found positive associations of maternal prepregnancy BMI with offspring bone size and density at the TBLH and spine, and our multivariable analyses and parental comparisons suggest that these relations are largely due to genetic
and environmental characteristics related to offspring adiposity in childhood and are unlikely to be attributable to an intrauterine mechanism. This conclusion is further supported by the fact that these associations are in the same direction as those that have consistently been shown between parental BMI and offspring BMI in childhood. Our study did not show clear beneficial effects of a higher maternal BMI during pregnancy on child bone mass. Given the known adverse health implications of higher maternal BMI for both the mother and offspring and the lack of any clear beneficial effects on offspring bone health, our findings further support women of reproductive age being encouraged to maintain a BMI within the normal range.

We are extremely grateful to all of the families who took part in this study, the midwives for their help in recruiting them, and the entire ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses.

The authors’ responsibilities were as follows—DAL: conceived and developed the idea for the study and supervised the analyses; and CM-W: completed the analyses and wrote the first draft of the manuscript. All authors contributed to the final interpretation of the results and the writing of the manuscript. The funding bodies did not influence the analysis protocol, the analysis, or interpretation of the results. No conflicts of interest were declared.

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