Gestational Weight Gain and Offspring Bone Mass: Different Associations in Healthy Weight Versus Overweight Women

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ABSTRACT

Weight management strategies during pregnancy reduce child cardiometabolic risk. However, because maternal weight has an overall positive correlation with offspring bone mass, pregnancy weight management could adversely affect child bone health. We aimed to estimate associations between gestational weight gain (GWG) and bone mineralization in the offspring at 7 years of age, and test early pregnancy body mass index (BMI) as an effect modifier. We analyzed prospective data from 2167 mother-child pairs from the Generation XXI birth cohort who underwent whole-body dual-energy X-ray absorptiometry at 7 years of age. GWG was analyzed as a continuous measure and using the Institute of Medicine categories. In the whole sample and for each early pregnancy BMI category (under/normal weight and overweight/obese), relationships between GWG and offspring bone measures (bone mineral content [BMC], bone areal density [aBMD], size-corrected BMC [scBMC], and height) at 7 years were fitted through local polynomial regression and smoothing splines. The magnitude of associations was estimated through linear regression coefficients (95% CIs), crude and adjusted for maternal age, height, educational level, and child gestational age. In under/normal weight mothers, GWG was associated with slightly increased bone measures at 7 years (per 5 kg of GWG, BMC: 0.07 SD [95% CI, 0.01 to 0.12]; aBMD: 0.10 SD [95% CI, 0.05 to 0.15], scBMC: 0.11SD [95% CI, 0.06 to 0.16], and height: 0.05 SD [95% CI, 0.00 to 0.10]), while in overweight/obese mothers no effect of GWG on bone was observed (BMC: 0.02 SD [95% CI, −0.04 to 0.09]; aBMD: 0.02 SD [95% CI, −0.04 to 0.08], scBMC: 0.01 SD [95% CI, −0.06 to 0.08], and height: 0.02 SD [95% CI, −0.04 to 0.08]). Also, no advantageous effect of gaining weight above the Institute of Medicine recommendations was observed in either early pregnancy BMI group. Our results suggest that adherence to Institute of Medicine recommendations for pregnancy weight gain is unlikely to have a negative repercussion on offspring bone health, particularly in women with excess weight in early pregnancy.

Introduction

The weight gained by women during pregnancy is an important and potentially modifiable determinant of short-term and long-term health outcomes for both the mother and the child.[1] Because its management is a key component of prenatal care, in 2009, the US Institute of Medicine (IOM) published revised guidelines for maternal gestational weight gain (GWG) according to early pregnancy body mass index (BMI) categories, where an overall inverse relation between baseline BMI and weight gain is recommended.[1–3] Those guidelines are now used as standard recommendations in the majority of high-income countries. Due to their policy nature, IOM guidelines overlook the heterogeneity of the associations between GWG and distinct health outcomes in terms of strength and direction.[4] For instance, although an inverted U-shaped association has been suggested for the effect of GWG on preterm birth, a monotonic dose-response association was described for GWG and birth weight, after adjustment for gestational age.[1] Heterogeneous associations have also been found for long-term child health outcomes, namely adiposity, cardiometabolic risk, and asthma.[5]

With regard to bone mass, there is evidence of positive effects of GWG on offspring bone mineral content (BMC) and areal

density (aBMD).[6,7] By altering the intrauterine environment, including nutrient availability or endocrine factors such as leptin and estrogen, GWG may influence not only fetal bone formation, but also the programming of bone strength during childhood and even later in life.[8,9] However, it seems plausible that the effect of GWG on offspring bone is qualitatively or quantitatively modified by prepregnancy maternal weight status. Particularly in view of the IOM guidelines for GWG—that recommend lower and narrower ranges of weight gain for overweight/obese women—possible implications of following those recommendations for the offspring's bone mineralization should be assessed and compared by prepregnancy BMI groups.

By means of a longitudinal study of children and their mothers within the Generation XXI birth cohort, our objective was to quantify the associations between GWG, continuously and using IOM recommended categories, and dual-energy X-ray absorptiometry (DXA)-derived bone measures and height of the offspring at 7 years of age. Specifically, we aimed to explore a possible modification of the effect of GWG on child bone mineralization by maternal early pregnancy BMI.

Materials and Methods

Generation XXI cohort assembly and follow-up

This study was based on the Generation XXI birth cohort whose full details have been published.[10,11] In 2005 to 2006, all women hospitalized for childbirth in one of the five public maternity units of Porto, Portugal, whose obstetric outcome was a live birth with at least 24 weeks of gestation, were eligible to participate. Of the invited mothers, 91.4% ($n = 8495$ women) accepted to participate and their 8647 infants were enrolled in the cohort study. In the 7-year-old follow-up wave (2012/2014), 67.6% of the cohort (5849 children) was reevaluated by face to face interview. This age represents as a biological milestone before the onset of puberty, when sexual development becomes a major driving force for growth and development, particularly regarding microarchitectural and macroarchitectural changes to the skeleton. Details of the cohort design and description of the cohort's baseline characteristics were provided as Supporting Data and Supporting Table 1.

The study protocol was approved by the Ethics Committee of Hospital de São João and registered with the Portuguese Authority of Data Protection and was carried out in accordance with the principles of the Declaration of Helsinki. In all evaluations written informed consent was obtained from parents or legal guardians and oral assent from children.

Measures of early pregnancy BMI and GWG

At baseline, within 72 hours after delivery, trained interviewers applied face-to-face structured questionnaires including data on demographic and socioeconomic characteristics, lifestyles, medical history, and anthropometrics. In the context of this large cohort comprising women recruited after delivery, the preferred method to collect weight throughout pregnancy was self-report by women. Besides feasibility, this option is supported by a previous systematic review showing that weight misreporting does not largely bias associations between pregnancy-related weight and birth outcomes.[12] To calculate early pregnancy BMI and GWG we used weight in early pregnancy as the baseline measure, defined as the self-reported weight in kilograms at the beginning of pregnancy

("What was your weight at the beginning of pregnancy?") or on the first prenatal medical visit ("What was your weight on the first pregnancy appointment?") if the latter occurred before the 13th gestational week. For women with missing information on this variable (6.0%), early pregnancy weight was recovered using either obstetric clinical records (0.6%) or the proxy question "What was your weight in the 2 years preceding pregnancy?" (5.4%). Clinical record review was planned with the purpose of recovering only data that were missing from the baseline questionnaire, which is why anthropometrics from this source is available only for a small number of participants.[13] Sensitivity analysis to assess the impact of using these different sources of information is described below. Predelivery weight was also obtained from the questionnaire ("What was your weight at the end of pregnancy?") or recovered from clinical records in the 3.1% of mothers with missing questionnaire information. Height was measured by the interviewer to the nearest 0.1 cm (55.4% of the mothers), abstracted from the national ID card when measurement was not possible (38.7% of the mothers) or recovered from clinical records (6.0% of the mothers). Early pregnancy BMI was calculated (weight/height [kg/m^2]) and categorized according to the standard World Health Organization (WHO) definition: underweight (<18.5 kg/m^2), normal (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2), or obese (≥30.0 kg/m^2).[14]

GWG was computed as the difference between the mother's self-reported predelivery weight and her early pregnancy weight. For 0.6% of the participants, GWG was recovered from the clinical record review. Women were categorized as gaining below (insufficient GWG), as recommended (adequate GWG), or above (excessive GWG) the IOM recommendations, as detailed in Table 1 footnote c.[1]

Child bone densitometry and anthropometric data

In the follow-up evaluation at the age of 7 years, all children assessed between December 1, 2012, and August 31, 2013, were consecutively invited to undergo a whole-body DXA scan (3015 children, 43.8% of the participants). Scans were performed using a Hologic Discovery QDR® 4500W device (software version 13.3.0.1; Hologic Inc., Bedford, MA, USA) according to standard manufacturer's protocol. Standard quality assurance tests were performed daily using the spine phantom according to manufacturer's instructions. The coefficient of variation obtained from repeated phantom measurements was below 1%. Scans were evaluated immediately after acquisition and later validated by a second technician with at least 5 years of experience. Total body less head BMC (g) and aBMD (g/cm^2) were obtained.[15] Size-corrected BMC (scBMC) was derived separately for girls and boys by linear regression of BMC on bone area and addition of the residuals of the regression to the mean sample BMC.[16] Weight and height were measured according to standard procedures and BMI was calculated. Height was also used in the present study as an outcome measure, as a proxy of linear growth of long bones.

Maternal and offspring neonatal data

Maternal age at delivery was recorded. Maternal educational level at the baseline evaluation was recorded as the number of completed years of education. Clinical records were reviewed at birth to retrieve data on birth weight and gestational age of the offspring.

Table 1. Maternal and Child Characteristics According to Groups of Early Pregnancy BMI

Characteristic	Whole sample (n = 2167)	Early pregnancy BMI groups[a]		p[b]
		Under/normal weight (n = 1392)	Overweight/obese (n = 775)	
Maternal characteristics				
Early pregnancy BMI (kg/m²), mean ± SD	24.4 ± 4.4	21.8 ± 1.9	28.9 ± 3.8	<0.001
Age at delivery (years), mean ± SD	29.9 ± 5.1	29.5 ± 5.0	30.7 ± 5.1	<0.001
Women by educational level, n (%)				<0.001
≤9 years	859 (39.7)	491 (35.3)	368 (47.5)	
10–12 years	624 (28.8)	385 (27.7)	239 (30.8)	
>12 years	682 (31.5)	514 (37.0)	168 (21.7)	
Missing	2	2	0	
Weight gain during pregnancy (kg), mean ± SD	13.2 ± 5.3	14.1 ± 4.9	11.7 ± 5.6	<0.001
Women by categories of gestational weight gain, n (%)[c]				<0.001
Insufficient	513 (23.7)	406 (29.2)	107 (13.8)	
Adequate	861 (39.7)	614 (44.1)	247 (31.9)	
Excessive	793 (36.6)	372 (26.7)	421 (54.3)	
Women with gestational diabetes, n (%)	126 (5.8)	58 (4.2)	68 (8.8)	<0.001
Missing	6	4	2	
Women who ever smoked during pregnancy, n (%)	450 (20.9)	313 (22.6)	137 (17.9)	0.010
Missing	15	7	8	
Child characteristics				
Gestational age at birth (weeks), mean ± SD	38.7 ± 1.6	38.7 ± 1.6	38.8 ± 1.6	0.184
Birth weight (g), mean ± SD	3197.6 ± 475.8	3167.0 ± 473.4	3252.5 ± 475.3	<0.001
Weight at 7 years, mean ± SD				
Crude (kg)	27.3 ± 5.5	26.4 ± 4.8	29.0 ± 6.2	<0.001
Z-score, WHO reference[d]	0.67 ± 1.14	0.48 ± 1.09	1.01 ± 1.17	<0.001
Z-score, Generation XXI reference[e]	0.02 ± 0.99	−0.15 ± 0.87	0.32 ± 1.10	<0.001
Height at 7 years, mean ± SD				
Crude (cm)	124.7 ± 5.6	124.4 ± 5.6	125.2 ± 5.6	0.002
Z-score, WHO reference[d]	0.30 ± 0.94	0.24 ± 0.94	0.40 ± 0.93	0.002
Z-score, Generation XXI reference[e]	−0.03 ± 0.99	−0.10 ± 0.99	0.08 ± 0.98	<0.001
BMI at 7 years, mean ± SD				
Crude (kg/m²)	17.4 ± 2.6	17.0 ± 2.2	18.3 ± 3.0	<0.001
Z-score, WHO reference[d]	0.68 ± 1.16	0.47 ± 1.08	1.06 ± 1.21	<0.001
Z-score, Generation XXI reference[e]	0.05 ± 0.99	−0.14 ± 0.84	0.38 ± 1.13	<0.001
Child DXA-derived bone measures at 7 years				
BMC, mean ± SD				
Crude (g)	597.4 ± 86.3	588.8 ± 84.2	612.7 ± 87.8	<0.001
Z-score, Zemel and colleagues (2011)[(17)] reference[f]	−0.04 ± 0.89	−0.14 ± 0.89	0.14 ± 0.86	<0.001
Z-score, Generation XXI reference[g]	0.00 ± 1.00	−0.10 ± 0.98	0.18 ± 1.02	<0.001
aBMD, mean ± SD				
Crude (g/cm²)	0.619 ± 0.056	0.612 ± 0.054	0.631 ± 0.056	<0.001
Z-score, Zemel and colleagues (2011)[(17)] reference[f]	0.40 ± 1.09	0.26 ± 1.07	0.66 ± 1.08	<0.001

continued

Table 1. (Continued)

Characteristic	Whole sample (n = 2167)	Early pregnancy BMI groups[a]		
		Under/normal weight (n = 1392)	Overweight/obese (n = 775)	p[b]
Z-score, Generation XXI reference[g]	0.00 ± 1.00	−0.12 ± 0.97	0.22 ± 1.02	<0.001
scBMC, mean ± SD				
Crude (g)	597.4 ± 39.6	592.9 ± 36.8	605.4 ± 43.1	<0.001
Z-score, Generation XXI reference[g]	0.00 ± 1.00	−0.12 ± 0.93	0.21 ± 1.09	<0.001

BMI = body mass index; BMC = bone mineral content; aBMD = areal bone mineral density; scBMC = size-corrected bone mineral content; GWG = gestational weight gain

[a]According to standard WHO definition.

[b]Values of p obtained for comparison between early pregnancy BMI groups (Wilcoxon rank or chi-square tests).

[c]According to the Institute of Medicine classification (2009): Insufficient: GWG <12.5 kg for underweight women, <11.5 kg for normal-weight women, <7 kg for overweight women, and <5 kg for obese women. Adequate: GWG of 12.5–18 kg for underweight women, 11.5–16 kg for normal-weight women, 7–11.5 kg for overweight women, and 5–9 kg for obese women. Excessive: GWG >18 kg for underweight women, >16 kg for normal-weight women, >11.5 kg for overweight women, and >9 kg for obese women.

[d]Age and sex-specific Z-scores computed using WHO reference data.[19]

[e]Age and sex-specific Z-scores computed based on the means and SDs derived from all Generation XXI participants in the 7-year-old follow-up wave with anthropometric data (n = 5838).

[f]Age and sex-specific Z-scores computed using the Bone Mineral Density in Childhood Study reference data.[17]

[g]Age and sex-specific Z-scores computed based on the means and SDs derived from the study sample (n = 2167).

Study sample

Of the 3015 children eligible for bone densitometry, 2408 had a valid DXA scan (79.9% of the eligible subsample) after excluding participants who refused to perform the scan and those whose images had unacceptable technical quality. For the current analysis, we additionally excluded children from multiple pregnancies (n = 111) and participants with no information on maternal GWG (n = 115) or without information to compute maternal early pregnancy BMI (n = 15) (Supporting Fig. 1). Additionally, we analyzed implausible values of GWG (less than 0 kg and more than 30 kg) and for six participants we recovered weights from an alternative source of information, among those previously described. The final sample comprised 2167 mother-child pairs (46.8% girls) whose comparison with the remainder of the cohort is presented in Supporting Table 2, which shows that study participants were more likely to present higher socioeconomic position than nonparticipants.

Data analysis

Given the frequency of underweight (3.1%) and obese women (10.4%), we combined the four early pregnancy BMI categories into two groups: (i) under/normal weight, and (ii) overweight/obese. Sensitivity analyses were conducted to test the robustness of that option. Maternal and child characteristics were compared between early pregnancy BMI groups with Wilcoxon rank-sum or chi-square tests. Age- and sex-specific Z-scores were computed for BMC and aBMD based on the method and reference values published by Zemel and colleagues.[17] We also computed internal Z-scores based on the means and SDs derived from the study sample (n = 2167), which was essential to obtain scBMC Z-scores. Age- and sex-specific weight, height, and BMI Z-scores were obtained according to WHO growth charts[18] and also using as reference all Generation XXI participants with anthropometric data at 7 years of age (n = 5838).

The shapes of the associations between GWG and bone parameters were assessed using local polynomial regression and smoothing splines (R packages *fANCOVA* and *splines*; R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/). Because the visual inspection of plots was consistent with linear relations, estimates of the magnitude of the associations between GWG and DXA-derived bone measures and height were obtained by using multiple linear regression coefficients and respective 95% confidence intervals (95% CIs). Results are presented per 5 kg increase in GWG to improve readability.

To assess whether the relationship between GWG and offspring bone mineralization was modified by maternal weight status, we stratified regression analyses by early pregnancy BMI groups. Analyses were conducted crude and adjusted for potential confounding factors, defined as documented causes of both GWG and child's bone mineralization and that are not likely to mediate their relationship: maternal age, height and educational level, and offspring gestational age.

Additional analyses with GWG defined as a categorical variable according to IOM categories were conducted by computing adjusted means of the offspring's BMC, aBMD, scBMC, and height using analysis of covariance (ANCOVA), adjusted for the previously defined potential confounders. The differences (95% CI) between those means in adequate versus insufficient and excessive versus adequate weight gain groups were estimated using Stata's postestimation command *lincom* (Stata Corporation, Inc., College Station, TX, USA).

Sensitivity analyses

To assess the effect of including the 6.0% of women whose early pregnancy weight was recovered from the alternative sources described (ie, clinical records or an alternative item on the questionnaire), we carried out a sensitivity analysis by recomputing estimates after excluding this group, and comparing these estimates with those obtained for the whole sample. Additionally, to assess the impact of misclassification due to self-reporting of weight, we recalculated estimates after excluding women classified as having higher susceptibility to weight underreporting according to published literature[19–23]; ie, participants with at least one of the following characteristics ($n = 641$ mothers): young maternal age (<25 years old), low educational level (<6 years), unmarried, late prenatal care (after the 12th gestational week), and higher parity (two or more previous pregnancies).

Statistical analysis and graphics were performed using Stata version 11.2 for Windows (Stata Corp) and R version 3.5.1 (The R Foundation for Statistical Computing).

Results

Maternal and child characteristics are presented in Table 1. At the beginning of pregnancy, 35.8% of the mothers were overweight or obese. In the whole sample, the mean ± SD maternal GWG was 13.2 ± 5.3 kg, greater in under/normal weight women than in women with excess weight (14.1 versus 11.7 kg, $p < 0.001$). More than one-third (36.6%) of children were born to women who gained excessive weight during pregnancy, according to the IOM recommendations, whereas 23.7% to women who had insufficient GWG. Women with higher BMI in early pregnancy had children with increased BMC, aBMD and scBMC at 7 years of age.

Fig. 1A–D presents the relationship between GWG and DXA-derived bone measures and height in the whole sample, including the plots of local polynomial regressions and smoothing splines, whereas Fig. 2A–D shows those relationships after stratification by early pregnancy BMI. When compared to smoothing splines, local polynomial regression showed higher variance in the ends of the GWG spectrum, as expected due to data sparsity. In under/normal weight mothers, visual inspection of the association between GWG and offspring bone suggests linear relations for all outcomes. After fitting linear regression models we estimated a modest positive slope, which persisted after adjustment for maternal age, height, educational level, and gestational age (β [95% CI]: BMC Z-score = 0.07 [95% CI, 0.01 to 0.12] per 5-kg weight gain; aBMD Z-score = 0.10 [95% CI, 0.05 to 0.15] per 5 kg; scBMC Z-score = 0.11 [95% CI, 0.06 to 0.16] per 5 kg; height Z-score = 0.05 [95% CI, 0.00 to 0.10] per 5 kg) (Fig. 3A–D). Nevertheless, the predictive performance of the model was low, with r^2 estimates between 1% and 2% for all bone measures. More important, however, among women with excess weight in early pregnancy, there were no linear associations between GWG and offspring DXA-derived bone measures or height (Fig. 2A–D), before or after adjustment for confounders (adjusted β [95% CI]: BMC Z-score = 0.02 [95% CI, −0.04 to 0.09] per 5-kg weight gain; aBMD Z-score = 0.02 [95% CI, −0.04 to 0.08] per 5 kg; and scBMC Z-score = 0.01 [95% CI, −0.06 to 0.08] per 5 kg; height Z-score = 0.02 [95% CI, −0.04 to 0.08]) (Fig. 3A–D). As expected, the fit of the model was very low, with r^2 estimates below 1%.

Within the under/normal weight group, and taking women with adequate GWG as the reference category, women with insufficient GWG had children with aBMD on average 0.14 SD (95% CI, 0.02 to 0.26) lower and scBMC 0.19 SD (95% CI, 0.07 to 0.30) lower at 7 years of age, after adjustment for confounders presented in Table 2. In contrast, in overweight women, no such relation was observed. Interestingly, for both early pregnancy BMI groups, there were no differences in mean bone measures between children born to women with excessive when compared to adequate GWG.

Sensitivity analysis

After restricting the analysis to participants whose information for weight in early pregnancy was collected from the primary source; ie, self-reported weight at the beginning of pregnancy or at the first medical appointment in the first trimester ($n = 2108$ [97.3%] of all mothers; $n = 1357$ [97.6%] of under/normal weight mothers; and $n = 751$ [96.9%] of overweight/obese mothers), the associations between GWG and offspring bone properties remained similar to those obtained including participants with alternative sources of information (Fig. 3A–D). Associations between GWG and offspring bone properties also remained essentially unchanged after restricting the analysis to mothers who were classified as having lower susceptibility to weight misreporting ($n = 1001$ [72.0%] of under/normal weight mothers and $n = 523$ [67.5%] of overweight/obese mothers) (Fig. 3A–D).

Discussion

In the present study, we found a modest direct linear association between maternal GWG and bone mineralization in the offspring of women who were under/normal weight in early pregnancy, possibly reflecting a weak biological effect. However, among overweight/obese women, increased GWG had no apparent relation with offspring bone mineralization. The corresponding causal interpretation would be that there is little or no apparent advantage of gaining excess weight during pregnancy for offspring bone health, particularly in women with excessive weight in early pregnancy. Our results were robust to different bone mineralization measures—DXA-derived or height—and different exposure definitions—GWG as a continuous variable or as IOM categories. Results remained practically unchanged after adjustment for maternal age, height and educational level, and gestational age of the offspring. Likewise, no relevant changes were found after excluding women whose weight was recovered from alternative sources or those more susceptible to weight misreporting.

Previous studies have looked at maternal body size during pregnancy and offspring bone.[6–9] Maternal fat stores during pregnancy were positively associated with offspring bone mineral and geometry at birth in the Southampton Women's Survey, particularly in late pregnancy.[8,9] With respect to weight changes, GWG was an independent predictor of BMD in 6-month-old infants from Generation R and in Chinese children aged 0 to 3 years.[6,7] In our study, we found evidence of a weak relationship between maternal GWG and childhood bone measures only among under/normal weight women. However, when stratified by IOM categories, there were no differences between mean bone properties between women gaining excessive and adequate weight, in contrast to the comparison between women gaining adequate and insufficient weight. This
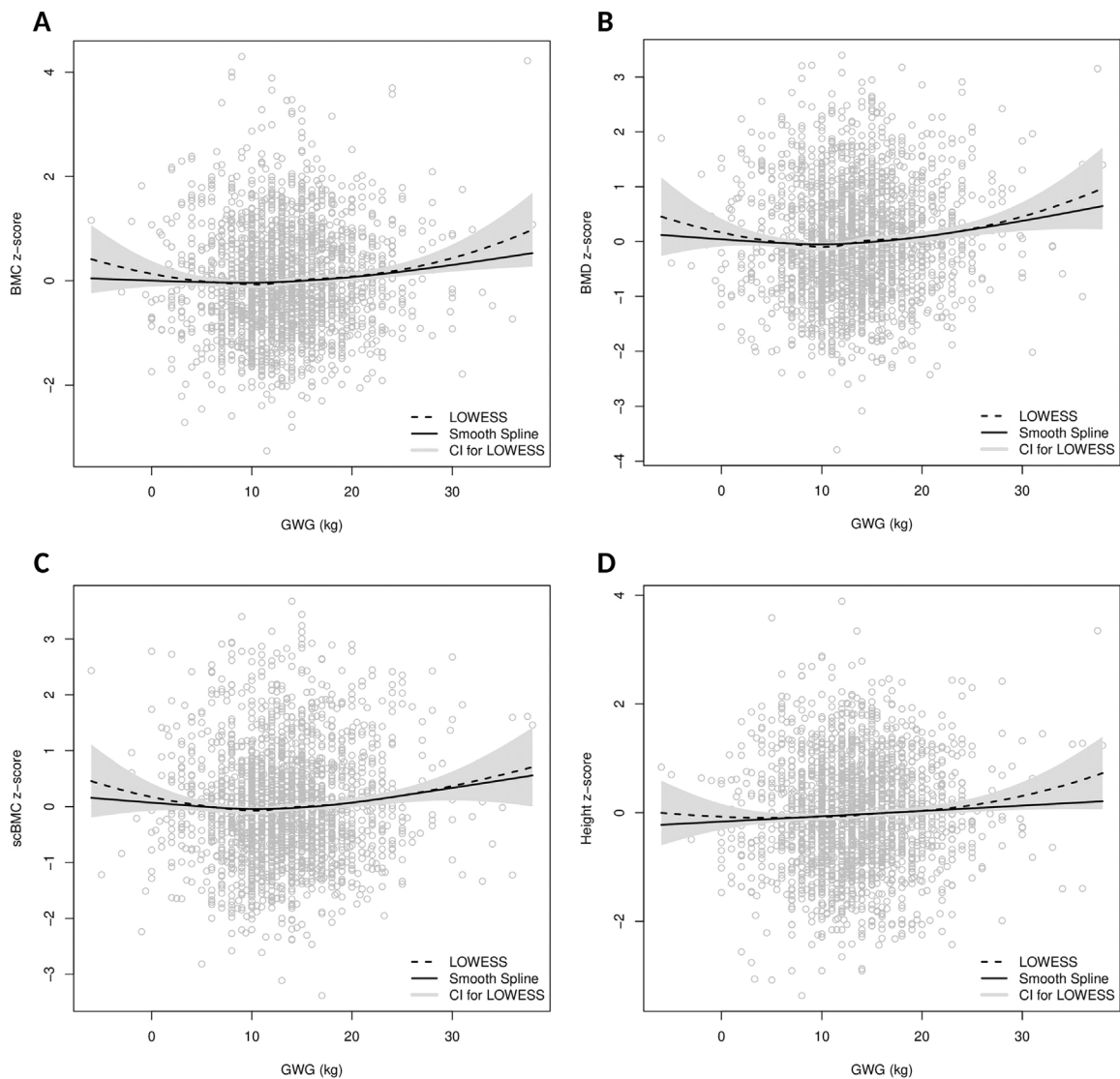
Fig. 1. Local polynomial regression and smoothing splines for gestational weight gain and offspring bone measures at 7 years. BMC (*A*), aBMD (*B*), scBMC (*C*), height (*D*). Dashed line, local polynomial regression; solid line, smoothing spline. aBMD = areal bone mineral density; BMC = bone mineral content; GWG = gestational weight gain; scBMC = size-corrected bone mineral content.

may be explained by either a relative lack of precision on the higher end of the GWG spectrum or a true leveling off of the biological effect with increasing GWG.

To the best of our knowledge, no studies have looked at the potential effect modification by maternal early pregnancy BMI on GWG-bone associations, even though GWG also showed greater impact on childhood overweight when mothers had normal versus excess weight before pregnancy.[24–27] Possible intrauterine mechanisms underlying a differential response of pediatric bone to GWG in low/normal BMI versus higher BMI in early pregnancy are several. First, differences in glucose metabolism profiles may contribute to a differential effect. When compared to overweight/obese women, under/normal weight women are less likely to have insulin resistance and/or impaired glucose tolerance during pregnancy,[28] and may be more sensitive to weight changes during gestation, inducing a more effective decrease in insulin sensitivity, followed by an augmented supply of nutrients to the fetus and enhanced bone

accretion.[29] Another possible mechanism may be related to chronic low-grade systemic inflammation associated with adiposity.[30,31] The placenta of obese women has increased number of macrophages and enhanced expression of proinflammatory cytokines interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and IL-6 in comparison with that of normal weight women[30] and low-grade inflammation in the higher BMI group may have restricted bone mineral accretion associated to GWG. Also, obese women are more likely to have low serum levels of vitamin D,[32] whose insufficiency has been associated with reduced bone mineral accrual.[33] Additionally, differences in weight or body composition trajectories according to early pregnancy BMI may also contribute to the discrepancy: in contrast to women with excessive weight at time of conception, higher weight gains during the second and third trimesters are more frequent in normal-weight women.[1,34] Because 80% of fetal bone mineral accumulation occurs during the last trimester of pregnancy,[35] greater weight gains later in pregnancy may
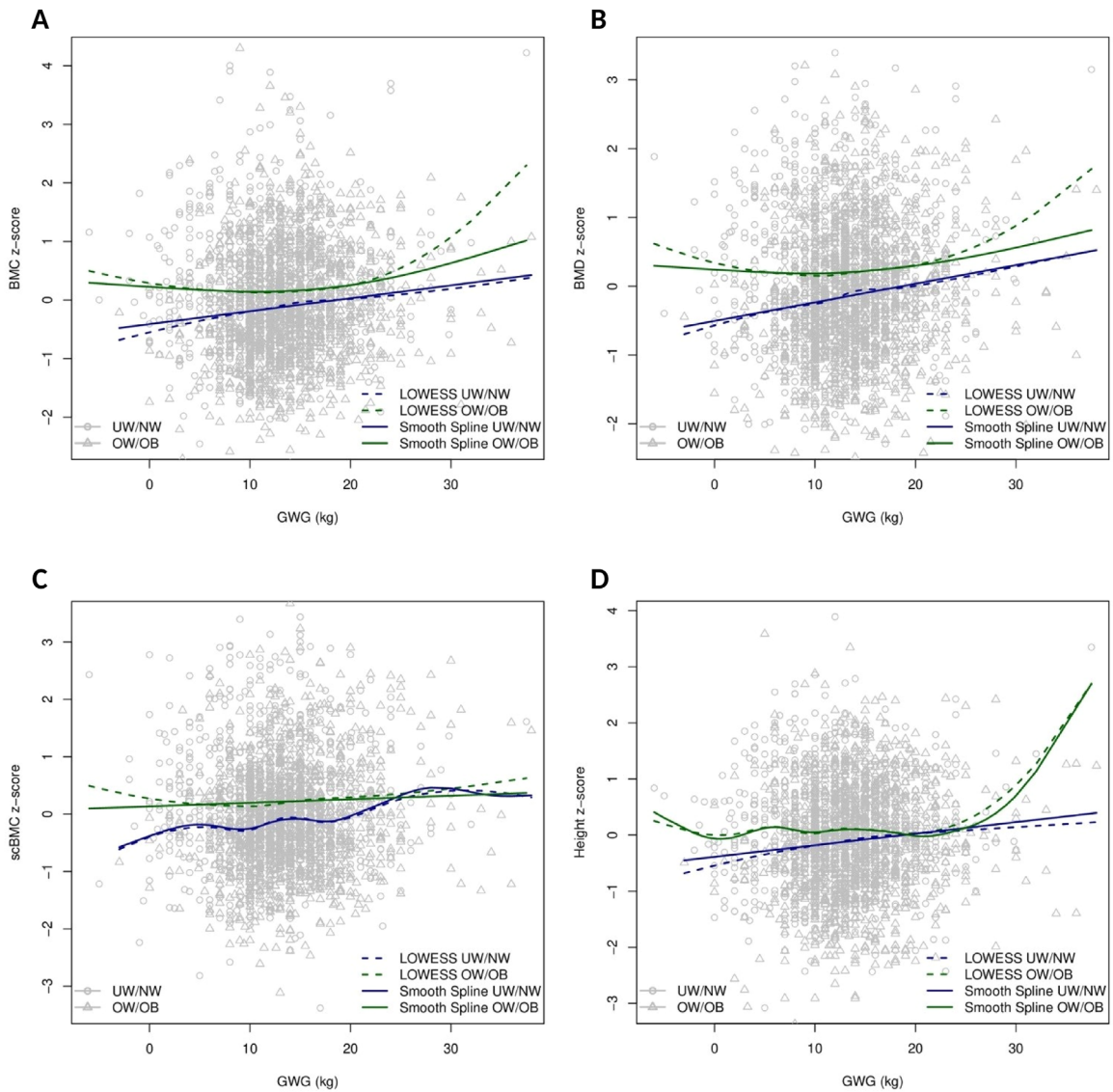
Fig. 2. Local polynomial regression and smoothing splines for gestational weight gain and offspring bone measures at 7 years, in under/normal weight and overweight/obese women. BMC (*A*), aBMD (*B*), scBMC (*C*), height (*D*). Dashed blue line, local polynomial regression in under/normal weight women; solid blue line, smoothing spline in under/normal weight women; dashed green line, local polynomial regression in overweight/obese women; solid green line, smoothing spline in overweight/obese women. aBMD = areal bone mineral density; BMC = bone mineral content; GWG = gestational weight gain; scBMC = size-corrected bone mineral content; UN/NW = under/normal weight women; OW/OB = overweight/obese women.

partially explain a positive association with offspring bone mass restricted to the low/normal BMI group. Also, under/normal weight women gain more fat than obese women, causing increased nutrient availability and greater exposure to hormones such as leptin and estrogen that may explain a clearer benefit of GWG on offspring bone.[9] Finally, we should not rule out the possibility that the absence of GWG-offspring bone associations in overweight women is attributable to a ceiling effect for bone mass change in response to weight gain due to the attainment of a weight level above which GWG no longer has an effect on intrauterine bone mineral accumulation.

Two artifactual explanations for our findings should also be considered. First, the heterogeneous effect of GWG on the offspring's bone by maternal BMI may have resulted from different GWG distributions. In comparison to overweight

women, mean GWG in under/normal weight women was higher, which may account for the positive GWG-offspring bone associations found in the latter group. However, we observed that heterogeneity by early pregnancy BMI remained similar throughout a wide range of GWG, from –1 kg to 37.5 kg (Supporting Fig. 2). Alternatively, different confounding structures in different strata of maternal BMI could have contributed to the differential associations observed. To rule out this explanation we tested different sets of potential confounders separately in each BMI group—maternal age, height, smoking during pregnancy, gestational diabetes, parity, maternal educational level and employment status, household income, offspring gestational age and sex—and we found that the associations of GWG with bone measures did not change regardless of the confounding structure tested (Supporting Tables 3 and 4).
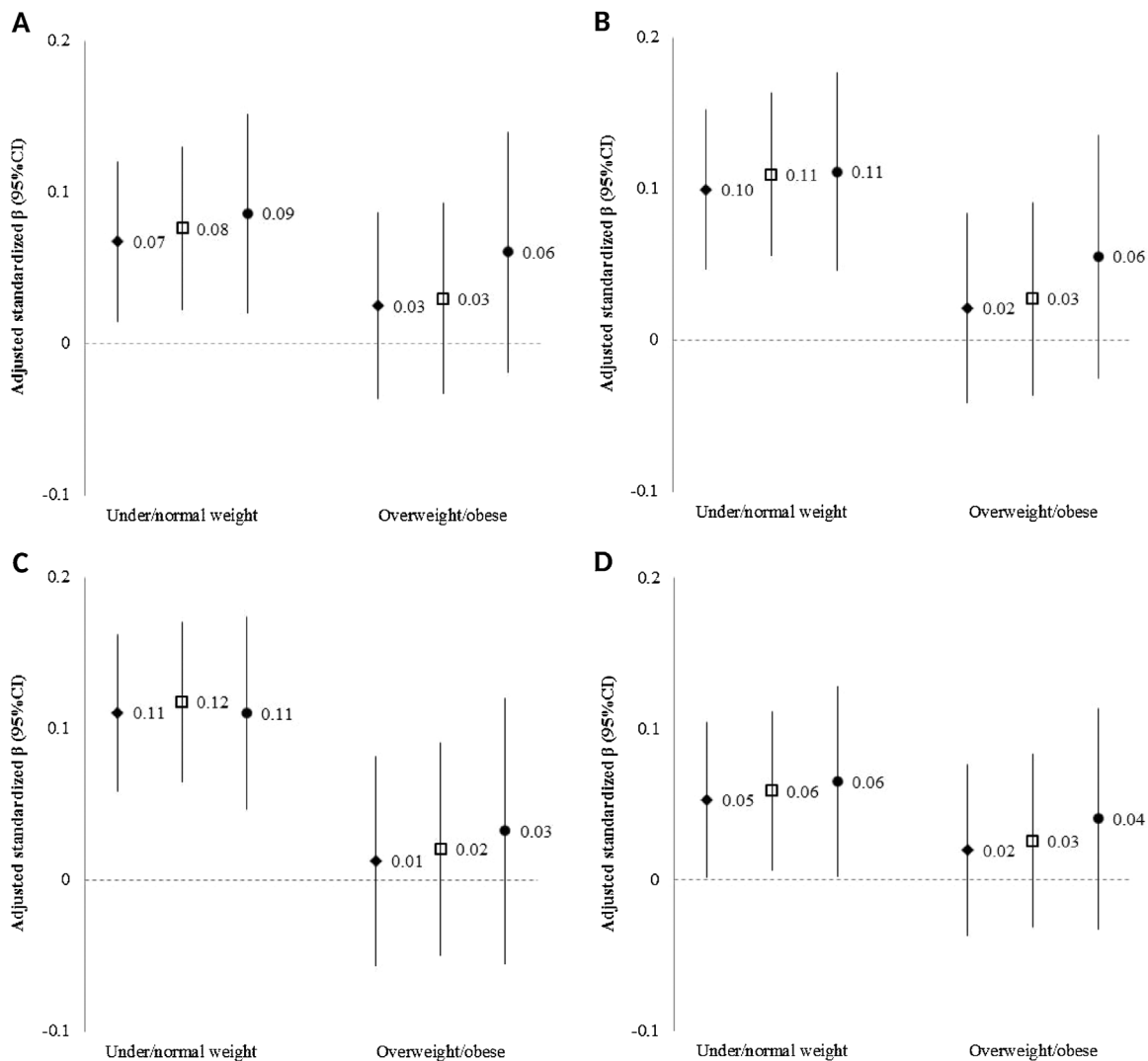
Fig. 3. Adjusted linear regression coefficients (95% CIs) for associations between gestational weight gain and offspring bone measures at 7 years in under/normal weight and overweight/obese women. BMC (*A*), aBMD (*B*), scBMC (*C*), height (*D*). Values are regression coefficients (95% CIs) that reflect the difference in standardized BMC, aBMD, scBMC, or height per 5-kg increase in gestational weight gain adjusted for maternal age, height and educational level, and gestational age at birth of the offspring. Diamond: whole sample (*n* = 1390 in the under/normal weight group; *n* = 775 in the overweight/obese group); square: only participants with information on self-reported weight in early pregnancy from the primary questionnaire source (*n* = 1357 in the under/normal weight group; *n* = 751 in the overweight/obese group); circle: only participants with lower susceptibility to weight misreporting (*n* = 1001 in the under/normal weight group; *n* = 523 in the overweight/obese group). aBMD = areal bone mineral density; BMC = bone mineral content; GWG = gestational weight gain; scBMC = size-corrected bone mineral content.

We used self-reported weight to compute BMI and GWG. This option might raise some concerns because there is evidence that women underestimate their early pregnancy weight, particularly those who are overweight before pregnancy.[36,37] To assess the potential impact of reporting bias on our effect estimates, we performed a sensitivity analysis by restricting the sample to women less likely to underreport their weight.[12,38] GWG-offspring bone associations in women less susceptible to misreporting were essentially similar to those obtained for the whole sample. Accordingly, results from previous studies have shown that reporting error does not significantly change associations between pregnancy-related weight and birth outcomes and that there is high agreement between self-reported and measured pregnancy weights when recall occurs within 1 year after delivery for early pregnancy weight and

within 6 weeks after delivery for predelivery weight,[12] as was the case in our study.

Although the vast majority of women (94.0%) had BMI and GWG estimated from self-reported weight in early pregnancy we opted to recover information from alternative sources for the remaining 6.0%. Our sensitivity analysis excluding the latter group showed that associations remained similar to those obtained for all participants. These results are consistent with previous evidence about agreement between data sources in Generation XXI, describing small differences between self-reported information and clinical records for pregnancy weight and height.[13]

DXA is a well validated and commonly used technique to assess bone density in children due to speed, precision, safety, low cost, and widespread availability. Because DXA does not provide a measure of true volumetric density,[15] we computed

Table 2. Adjusted Means ± SD of Z-scored Bone Mass Properties at 7 Years of Age, According to Maternal GWG Categories (Institute of Medicine, 2009), in Under/Normal Weight and Overweight/Obese Women

	Adjusted (mean ± SD)			Differences means (95% CI)	
	Insufficient GWG	Adequate GWG	Excessive GWG	Adequate − insufficient GWG	Excessive − adequate GWG
BMC Z-score					
Under/normal weight	−0.19 ± 0.05	−0.09 ± 0.04	−0.00 ± 0.05	0.10 (−0.02 to 0.22)	0.09 (−0.03 to 0.21)
Overweight/obese	0.22 ± 0.09	0.16 ± 0.06	0.18 ± 0.05	−0.05 (−0.28 to 0.17)	0.02 (−0.13 to 0.17)
aBMD Z-score					
Under/normal weight	−0.25 ± 0.05	−0.11 ± 0.04	0.00 ± 0.05	0.14 (0.02 to 0.26)	0.12 (−0.00 to 0.24)
Overweight/obese	0.24 ± 0.10	0.20 ± 0.06	0.23 ± 0.05	−0.04 (−0.27 to 0.18)	0.02 (−0.13 to 0.18)
scBMC Z-score					
Under/normal weight	−0.27 ± 0.05	−0.08 ± 0.04	0.00 ± 0.05	0.19 (0.07 to 0.30)	0.08 (−0.04 to 0.20)
Overweight/obese	0.19 ± 0.11	0.20 ± 0.07	0.22 ± 0.05	0.00 (−0.24 to 0.25)	0.02 (−0.15 to 0.19)
Height Z-score					
Under/normal weight	−0.17 ± 0.05	−0.11 ± 0.04	0.01 ± 0.05	0.06 (−0.05 to 0.18)	0.12 (0.00 to 0.24)
Overweight/obese	0.03 ± 0.09	0.07 ± 0.06	0.10 ± 0.04	0.04 (−0.16 to 0.24)	0.03 (−0.11 to 0.17)

Means are adjusted for maternal age, height, educational level, and gestational age at birth of the offspring.
GWG = gestational weight gain; BMC = bone mineral content; aBMD = areal bone mineral density; scBMC = size-corrected bone mineral content.

and used scBMC as an approximation of volumetric BMD,[39,40] and we also tested height as an outcome. We did not collect data on in vivo reproducibility to avoid repeated exposure of children to radiation.

This study is strengthened by the use of data from a large prospective population-based birth cohort, assembled during a short period of time, thereby avoiding confounding by age or birth cohort effects. However, we observed differences in maternal characteristics between participants included and the remainder of the cohort that pose a challenge for the generalizability of the findings to the whole cohort. Nevertheless, in our setting the most important correlates of nonparticipation at baseline and attrition throughout follow-up are also determinants of weight misclassification recognized in published literature. Such determinants, including maternal age and educational level, have been considered in our sensitivity analyses to assess the impact of weight misclassification, which was minor. If those findings are extrapolated to the potential impact of attrition and nonparticipation, it seems plausible that our estimates are not substantially biased, which would be compatible with a biological rather than socially-patterned effect of GWG on child bone. A related subject is the generalizability of our findings. Generation XXI is comparatively homogeneous in terms of geographical origin, because only 4.5% of mothers are first-generation immigrants and 3.5% from non-European countries.[41] This background may limit generalizability to other settings, even though our estimates remained essentially unchanged after excluding women born outside the country (data not shown).

In this study we estimated heterogeneous associations between GWG and offspring bone mineralization according to maternal early pregnancy BMI, suggesting a biological interaction between early pregnancy nutritional status and subsequent trajectory. Given the well-known adverse implications of excessive GWG for both mother and offspring on a wide range of outcomes, our findings support that women who are encouraged to follow IOM weight gain recommendations during pregnancy should not expect a deleterious effect on the child's skeletal health.

At the policy level, our findings reinforce IOM guidelines for weight gain. At the clinical practice level, this study supports the inclusion of bone health in the context of weight counseling during pregnancy.

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