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Rapid Infant Weight Gain and Advanced Skeletal Maturation in Childhood

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Abstract

Objective—To test the hypothesis that rapid infant weight gain is associated with advanced skeletal maturity in children from the United States and South Africa.

Study design—Longitudinal data from 467 appropriate-for-gestational-age infants in the Fels Longitudinal Growth Study (Dayton, Ohio) and 196 appropriate-for-gestational-age infants in the Birth to Twenty birth cohort study (Johannesburg, South Africa) were used. Multiple linear regression models tested the association between internal SD score change in weight from 0 to 2 years and relative skeletal age at 9 years, adjusting for body mass index, stature, and other covariates.

Results—In both studies, faster infant weight gain was associated with more advanced skeletal maturity (approximately 0.2 years or 2.4 months per SD score) at age 9 years ($P < .0001-.005$), even when adjusting for the positive associations of both birth weight and body mass index at age 9 years. This effect appeared to be accounted for by the greater childhood stature of subjects with more rapid infant weight gain.

Conclusions—Relatively rapid infant weight-gain is associated with advanced skeletal development in late childhood, perhaps via effects on stature.

Infants with rapid weight gain in the first 1 to 2 years of life have twice the risk of obesity¹ and greater central adiposity^{2,3} compared with infants with more gradual weight gain. Rapid infant weight gain is also associated with insulin resistance and beta-cell dysfunction⁴⁻⁶ in childhood and cardiovascular disease risk in adulthood.⁷ Furthermore, there is evidence that girls who experience rapid weight gain in infancy have an earlier age at menarche than girls with slower weight gain.⁸⁻¹⁰ Because girls with earlier menarche also tend to become obese,¹¹⁻¹³ rapid infant weight gain may be an early sign that an individual is on a trajectory toward both accelerated maturation and obesity. However, there are no published studies linking infant weight gain to developmental advancement in boys. Skeletal age is an indicator of physical development that can be used to examine the relationship between infant weight gain and the rate of maturation in both sexes.

An observed clustering of slow intrauterine growth, rapid postnatal growth, earlier menarche, and adverse metabolic outcomes has been explained using life history theory as an evolutionary trade-off between growth in size and reproductive success when poor maternal nutritional status signals the presence of a constrained growth environment.¹⁴ Under this model, accelerated development during periods of nutritional bounty may slightly increase the reproductive lifespan and thereby create positive selection. In this circumstance, it would be expected that the relationship between infant weight gain and the rate of physical and sexual maturation would be strongest in contexts in which prenatal growth is slow and post-natal growth is very rapid. However, the differing effect of rapid infant weight gain on the tempo of growth and maturation in children in more or less constrained growth environments has not been formally tested.

With prospective data on infant and childhood growth and skeletal maturation in birth cohorts from the United States and Johannesburg, South Africa, this study addresses the hypothesis that rapid infant weight gain is associated with advanced childhood skeletal maturity across widely contrasting environmental circumstances, independent of birth weight, childhood body mass index (BMI), and body size (stature).

Methods

This study used longitudinal data from 2 cohorts; The Fels Longitudinal study (FLS), set in Dayton, Ohio, and Birth to Twenty study (Bt20), set in Johannesburg-Soweto, South Africa. The FLS began in 1929 as a study of individual variation in the growth and development of children. Birth year varied from 1929 to 1997 in the study sample, and therefore birth year was included as a covariate in all models. The FLS sample included 467 white children (245 boys, 222 girls) born to families in the Dayton region, who had birth weights appropriate for their gestational age (AGA). The 467 children in this analysis comprise 69% of male and 67% of female children seen throughout childhood in the FLS, with the remainder excluded because they lacked either birth weight (because of a home birth or unavailable birth record) or weight at age 2 years or age 9 years (because of missing data at those specific ages). There were no differences in birth weight, height at 9 years, or BMI at 9 years between FLS children who were in this analysis and FLS children not in the analysis. FLS did not collect sexual maturity data until after 1985, but growth curve data were used to estimate their likely sexual maturity status.^{15,16} Most of the 467 children (61%) were pre-pubertal at their age 9 visit (ie, were seen before their pre-pubertal minimum height velocity), 34% were in early puberty (ie, were seen at least 2 years before their peak height velocity), and 5% were in early-mid puberty (ie, were seen 1-2 years before their peak height velocity). All protocols and informed consent materials were approved by the Wright State University Institutional Review Board.

Bt20 aims to investigate the relationship between child health and urbanization and initially sampled 3273 births (including 2568 black children) that took place from April 23 to June 9, 1990, to mothers with a permanent address in the Soweto-Johannesburg conurbation, South Africa. The Bone Health substudy of Bt20 was initiated in 1999 to investigate bone health during adolescence (from age 9 years to maturity). The Bone Health substudy included 401 children of African (black) ethnicity who had been seen at earlier Bt20 assessments. This study drew 196 children (109 boys, 87 girls) from the 401 (49%) who were AGA and had complete data at birth, 2 years, and 9 years, including a hand-wrist x-ray. Black children in Bt20 were chosen to form a clear contrast to the sample of non-Hispanic white children in the FLS. This subset was not significantly different from all 401 black children in the Bt20 Bone Health substudy nor from the 2568 black children in the entire Bt20 cohort in height, weight, or BMI at age 2 years or age 9 years. Birth weight in the analysis sample was slightly higher than that in the excluded cases (3.18 versus 3.08 kg in the entire Bt20 cohort, $P < .001$; and 3.18 versus 3.03 kg in the Bt20-Bone Health study, $P = .003$). Most Bt20 children were pre-pubertal at age

9 years (79.5%), and the remainder were in Tanner stage 2 (20.5%). All protocols and informed consent materials for the Birth to Twenty Study were approved by the Institutional Review Boards and Research Committees of Loughborough University and the University of Witwatersrand.

Measurements

Gestational age at birth (range, 37-42 weeks) was calculated from maternal report of last menstrual period and was entered in all models as a continuous covariate. Maternal age and parity were obtained via interview or from obstetric records. Both studies used standard anthropometric techniques^{17,18} for length (height) and weight at birth, age 2 years, and age 9 years. Infants were weighed in the hospital at birth in both studies, and then at 2 and 9 years of age at the study center (FLS) or at home (Bt20). The prevalence of stunting (height for age >2 SD scores [SDS] below the median) was determined at age 2 years as recommended by using the NCHS/World Health Organization reference data and ANTHRO software (version 1.02, 1999; World Health Organization, Geneva, Switzerland). For analysis, weight (kg), height (cm), and BMI (kg/m^2) at birth, 2 years, and 9 years were converted to SDS by using internal sex- and age-specific sample mean weight and SD for each study. "Infant weight gain" was calculated as the difference between weight SDS at birth and 2 years. Infant weight gain was used primarily as a continuous variable, but we also categorized infants as having "rapid" and "slow" infant growth according to the definition of Ong et al² of "clinically significant" weight increment between birth and 2 years greater than $+0.67$ SDS (rapid) or less than -0.67 SDS (slow). A 0.67 SDS change corresponds approximately to a change in 1 major centile band (eg, 25th -50th, 50th-75th, etc) on a weight-for-age growth chart. Change in weight SDS score from birth to 1 year of age was strongly correlated with change in weight SDS from birth to 2 years in the FLS ($r = 0.875$; $P < .0001$), and 77% of infants were categorized in the same infant weight gain group (slow, no change, or fast) by using weight SDS at 1 year or weight SDS at 2 years. We chose to use age 2 years data because this maximized our sample sizes for analysis. In the FLS only, height (cm) at age 20 years was used to test whether effects of rapid infant weight gain on the rate of skeletal maturation forecasted shorter adult stature.

We chose internal, study-specific growth references rather than external references for the calculation of the SDS because this provided equally sensitive measures of growth rate variation in each context; using a single international reference would reduce the number of Bt20 children with "rapid" weight gain and thus diminish statistical power to detect the association with relative skeletal age. We reanalyzed the data with a single international reference for both studies (the CDC 2000 growth curves¹⁹) and found similar results (data not shown), except that the associations in Bt20, although remaining significant, were diminished in magnitude.

Skeletal maturity of the hand-wrist was determined at 9 years of age using the Fels method²⁰ in the FLS study and the Tanner-Whitehouse 2 method²¹ (TW2) in the Bt20 study. Inter-rater technical error was very low in both studies (0.08 years in FLS and 0.26 years in Bt20). Studies comparing the TW2 with Fels techniques for skeletal maturity assessment suggest TW2 skeletal ages to be in advance of Fels skeletal ages in both male and female subjects by an average of 0.1 to 0.9 years (see for example²²). There is evidence that the method differences are relatively small and not statistically significant in the pre-pubertal age range examined here²³; however, we initially stratified all analyses by cohort to avoid possible measurement bias caused by differing skeletal age assessment methods. The data were then pooled to test the difference in the relationship between infant weight gain and relative skeletal age in the 2 studies (see below). Because the children were seen in a range of chronological ages (8.45-9.99 years), we adjusted skeletal age for the chronological age at which it was determined for each child; relative skeletal age was calculated by subtracting chronological

age from skeletal age. Children with positive relative skeletal age values were relatively more advanced in skeletal development, and children with negative values were more delayed in skeletal development.

Statistical Analysis

We used χ^2 tests for frequencies and independent sample t tests for continuously distributed variables to assess significant differences between boys and girls within and between studies; Bonferroni corrections were made to reduce the risk of inflated type 1 error. To illustrate the effects of rapid versus gradual and slow infant growth on BMI, height, and skeletal age at age 9 years, analysis of covariance models were used to generate least squares mean estimates (and accompanying standard errors), adjusting for sex, maternal age, parity, gestational age of the infant, birth weight SDS, and, for FLS only, year of birth, by using PROC GLM in SAS software (version 9.1; SAS Institute, Cary, North Carolina). Multivariate linear regression models were constructed for FLS and Bt20 to examine the association between change in infant weight SDS from 0 to 2 years and relative skeletal age at 9 years with the Statistical Package for the Social Sciences software (SPSS; version 16.0, SPSS, Chicago, Illinois). In all models, sex, gestational age, parity, maternal age, and birth year (FLS only) were included. Additional models included birth weight SDS, year 9 BMI SDS, and year 9 height SDS. Independent variables were examined for collinearity with one another, and all were correlated with all others at $r < 0.7$, and the variance inflation factor was also examined to determine multicollinearity. To test for significant differences in the effect of infant weight SDS changes on relative skeletal age by birth weight, an interaction term (infant weight SDS change*birth weight SDS) was added to the model. Sex differences in the effect of infant weight SDS change on relative skeletal age were tested first by observation of the estimates from sex-stratified models, and because the estimates were similar in both sexes, an interaction term was then tested with sexes combined (sex*infant weight SDS). Similarly, we compared the results between the studies first by informally comparing the beta coefficients from the models and then formally tested the significance of differences across each study by pooling the data and adding an interaction term to the model (ie, study*infant weight gain SDS).

Results

Descriptive statistics for the 2 samples are found in Table I. As expected, there were many differences between Bt20 and FLS children in their early growth and nutritional status. In general, the South African children were smaller, with lower birth weight, weight at age 2 years, and particularly height at age 2 years. Approximately 17% of Bt20 children were stunted at age 2 years, compared with none of the FLS children. Mean BMI was higher in Bt20 children compared with FLS children at age 2 years, particularly in girls. By age 9 years, however, weight, height, and BMI SDS were not significantly (or only marginally significantly) different in the 2 samples. Mean relative skeletal age at 9 years was not different from 0 ($P > .05$) in the FLS boys and girls and in the Bt20 girls, indicating no delay in skeletal maturation relative to the Fels and TW2 reference populations, respectively. However, relative skeletal age was delayed in the Bt20 boys by approximately 0.50 years.

Our primary aim was to examine the relationship of rate of infant weight gain to skeletal maturity in late childhood (Table II). In both studies, a greater increase in weight SDS from 0 to 2 years was associated with more advanced skeletal maturity at age 9 years ($P < .0001-.005$), even when adjusting for the positive and significant association of both birth weight and BMI at age 9 years with skeletal maturity. The magnitude of the effect was similar across studies: for each SDS increase in weight from 0 to 2 years, skeletal age was advanced by approximately 0.2 years (2.4 months). There was no indication that the positive effect of infant weight gain on the rate of skeletal maturation differed in boys and girls or by birth weight,

because these interaction effects were all non-significant (data not shown). Although the difference in skeletal age assessment methods requires caution in pooling the data, significant interaction effects between study and infant weight gain were tested and not found ($P > .7$ for all models tested). The Figure illustrates this association by comparing BMI, height, and skeletal age at age 9 years in children with rapid, gradual, and slow infant weight gain; in addition to being approximately 0.7 years more advanced in skeletal development, children who had experienced rapid infant weight gain were also approximately 8 cm taller and 2 to 3 BMI units heavier than children with slow infant weight gain.

As expected, height was strongly associated with relative skeletal age, and when it was added to the model (Table II, model 4), the effect of infant weight gain became non-significant in Bt20 and reversed sign in FLS. Because of the clinical concern with short final stature in the rapidly maturing child, we examined height at age 20 years (available in the FLS only); children who had experienced rapid infant weight gain were taller than children who had experienced slow infant weight gain in both sexes (+6 cm, $P < .0001$ in male subjects and +5 cm, $P = .0004$ in female subjects).

Discussion

Infancy has long constituted a vulnerable period of life, and therefore robust infant weight gain is generally viewed as a sign of child health and well-being. However, in the United States, Europe, and elsewhere, where the prevalence of maternal obesity is increasing²⁴⁻²⁶ and the childhood rate of overweight and obesity is high,^{27,28} attention is shifting toward the possible adverse effects of very rapid infant weight gain, including obesity and its metabolic and cardiovascular sequelae.^{2,7}

The novel finding in this study was that among AGA infants, rapid infant weight gain was associated with advanced skeletal development in later childhood, independent of its associations with birth weight and higher childhood BMI. In both studies, skeletal age in children whose weight SDS increased significantly (defined as >0.67 SDS units) from birth to age 2 years was approximately 7 months more advanced than in children whose weight SDS declined significantly in the same period, an effect beyond the level of skeletal assessment measurement error in either study. This extends and generalizes the finding that rapid infant weight gain is associated with advanced sexual maturation (menarche) in girls⁸⁻¹⁰ to show that rapid infant weight gain is associated with advanced physical maturation in children of both sexes. An earlier report from the Bt20 study did not find this association,²⁹ but that analysis did not include adjustment for sex, age, birth weight, or BMI, which may have diminished precision, and only compared infants with rapid weight gain to all other infants, which reduced power.

It has been posited that the widely replicated association of rapid infant weight gain with later health outcomes stems from a mismatch between prenatal metabolic cues and post-natal nutritional conditions.^{14,30} Because of their lower average birth weight and the marked post-Apartheid nutrition transition occurring in South Africa during this period,³¹ the Bt20 cohort might have been expected to demonstrate a stronger association of infant weight gain to later outcomes than the FLS cohort, but the observed relationships were of similar magnitude across studies. A recent review article³² pointed out that the impact of early postnatal growth variation on later health may differ depending on the nutritional context, but that few studies have explicitly tested this hypothesis. As expected, the absolute magnitude of “rapid” infant weight gain was greater in the FLS than the Bt20 children (ie, 1 SDS increase in infant weight gain was equivalent to 0.82 kg in FLS and 0.59 kg in Bt20). However, the similarity in the effect in a well-nourished population with documented stable growth and sexual maturation in girls in the 20th century³³ and an urban African population characterized by a high rate of linear

growth stunting suggests that this phenomenon is not entirely dependent on the nutritional status of the population. The children in this analysis were all AGA at birth, and there was no interaction of infant weight gain with birth weight, further indicating that the effects of post-natal “catch-up” growth (referred to here more generally as “rapid infant weight gain”) on childhood growth and development traits are not particular to small or growth-restricted infants.

Alternatively, or in addition, infants who move upward across major weight centiles during the first 2 years of life may have a greater genetic growth potential. In the FLS, >80% of the variance in infant weight gain³⁴ and >90% of the variance in infant recumbent length gain in the first 2 years³⁵ is attributable to additive genetic effects. The rate of skeletal maturation is also highly heritable and shares genetic covariance with height.³⁶ In general, growth traits are moderately to strongly heritable in populations worldwide.³⁷ Previously unrecognized environmental exposures, resulting in epigenetic modification of the DNA, may also affect the expression of genes regulating growth rate and maturation.³⁸ As Must13 observed, childhood obesity may be generally “auxogenic” (growth-promoting) in that the excess calories driving obesity also drive increased growth rate. The converse may also be true (increased linear growth rate may drive obesity); a recent study in the CATCH cohort³⁹ found that at age 8 years, taller overweight children had a greater risk of obesity developing in adulthood than shorter overweight children, and they remained taller in adulthood (unpublished results). Greater pre-pubertal stature does not, therefore, “protect” children from long-term obesity risk, but is instead an obesity risk factor. The relationship of infant weight gain to accelerated biological maturation, obesity, and chronic disease risk may not only result from restricted in utero growth followed by postnatal nutritional excess, but also via development programs pre-disposing to rapid linear and weight growth interacting with as yet unknown early environmental exposures to dis-regulate appetite and energy intake.

Our study pointed out that the relationship of infant weight gain to skeletal maturity in late childhood is highly influenced by height. Although not collinear in the formal sense (variance inflation factor <3 in both studies for all variables), infant weight gain was correlated with childhood height ($r = 0.23$ in Bt20 and $r = 0.34$ in FLS). When all 3 factors were accounted for in our models, the association with skeletal maturity was reduced in Bt20 and strengthened and reversed sign in FLS. The reversal in sign in the FLS is difficult to interpret. Our interpretation is that rapid infant weight gain, advanced skeletal maturity, taller stature, and higher BMI are all part of a correlated pattern, and when all variables are simultaneously in the model, the stronger association of concurrent height with skeletal age alters the weaker association of infant weight gain with skeletal age, suggesting that the effect of rapid infant weight gain on skeletal development works through its effect on linear growth rate. The children in the Bt20 study are only now reaching adult stature, and so whether the greater skeletal maturity and height seen at age 9 years foretells an earlier and shorter adolescent growth spurt and shorter adult stature in children with rapid infant weight gain is yet to be determined. However, this was not found in the FLS children; the greater height at age 9 years in children with rapid infant weight gain continued to age 20 years.

Because the South African black children in the study were exposed to a profoundly different nutritional environment than the non-Hispanic white children in this analysis, we cannot infer from the similar results across cohorts that race/ethnicity has no effect on the relationships. We cannot assume that findings would be similar, for example, in African American children (who tend to mature faster than European American children). This constitutes a limitation in the application of our findings to other ethnic groups and populations. However, this approach also represents a strength of the study, because there are few other studies that have directly compared the relationship of early growth with later developmental outcomes internationally. In neither cohort were recumbent length or markers of skeletal development consistently

available at birth, so it is possible that the greater childhood skeletal maturity and height of rapidly growing infants (considered outcomes, in this analysis) may actually have predated the infant weight gain (considered a determinant, in this analysis). Therefore, we are careful to frame our findings in the context of statistical, rather than causal associations.

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Glossary

AGA	Appropriate for gestational age
Bt20	Birth to Twenty study
BMI	Body mass index
FLS	Fels Longitudinal study
SDS	SD score
TW2	Tanner-Whitehouse 2 method

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Figure.

BMI, height, and skeletal age at age 9 years by infant weight gain group in 467 white children in the Fels Longitudinal Study, and 196 South African black children in the Birth to Twenty.

Table 1
Characterization of study cohorts: Fels Longitudinal Study and Birth to Twenty

Variable	Fels Longitudinal Study		Birth to Twenty		Study differences [*]	
	Boys	Girls	Boys	Girls	Boys	Girls
N	245	222	109	87	-	-
Gestational age at birth (weeks)	39.79 (1.37)	39.80 (1.65)	37.89 (1.53)	37.99 (1.78)	<.0001	<.0001
Birth weight (kg)	3.54 (0.42)	3.40 [†] (0.44)	3.25 (0.48)	3.09 [‡] (0.34)	<.0001	<.0001
Weight at 2 years (kg)	12.59 (1.22)	11.99 [†] (1.24)	11.77 (1.78)	11.46 (1.51)	<.0001	.002
Height at 2 years (cm)	88.02 (3.06)	87.08 [†] (2.97)	83.71 (4.13)	82.34 [§] (3.34)	<.0001	<.0001
BMI at 2 years (kg/m ²)	16.22 (1.11)	15.78 [†] (1.12)	16.81 (2.22)	16.92 (2.04)	.010	<.0001
Stunted [¶] at 2 years (%)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	17.35 (9.85-24.84)	12.00 (4.65-19.35)	<.0001	<.0001
Weight change 0-2 years (kg)	9.04 (1.19)	8.59 [†] (1.18)	8.52 (1.70)	8.37 (1.49)	<.0001	.175
Weight at 9 years (kg)	30.73 (6.11)	29.82 (5.63)	29.41 (4.85)	29.91 (6.77)	.047	.902
Height at 9 years (cm)	134.65 (5.33)	133.82 (5.41)	133.41 (5.76)	132.89 (5.59)	.050	.179
BMI at 9 years (kg/m ²)	16.87 (2.63)	16.57 (2.36)	16.47 (1.99)	16.82 (2.89)	.160	.425
Skeletal age at 9 years (years)	8.99 (1.15)	9.11 (1.02)	9.03 (0.73)	9.39 [‡] (1.07)	.706	.038
Relative skeletal age at 9 years (years) ^{¶¶}	-0.01 (1.10)	0.11 (1.02)	-0.49 (0.70)	-0.13 [‡] (0.98)	<.0001	.066
Maternal age at birth (years)	29.11 (5.55)	28.10 (5.88)	25.17 (5.97)	24.77 (6.13)	<.0001	<.0001
Term births (%)	91.43 (87.92-94.93)	90.09 (86.16-94.02)	88.99 (83.11-94.87)	84.09 (76.45-91.73)	.466	.209
Primiparity (%)	31.40 (25.56-37.25)	31.36 (25.23-37.49)	39.45 (30.27-48.62)	52.87 (42.38-63.36)	.141	.009

Mean (SD) for continuous variables and % (95% CI) for categorical variables.

^{*} *P* values from independent sample *t* tests comparing means for boys and girls within study and between studies within sex for continuous variables and from χ^2 tests of proportions for categorical variables.

[†] *P* < .0001.

[‡] *P* < .01.

[§] *P* < .05.

¶ Stunted children were identified at 2 years of age by using a definition of a height-for-age z-score >2 SDs below the median for the 1976 NCHS reference population for the appropriate sex and age.

// Relative skeletal age at 9 years is the skeletal age at 9 years minus the exact chronological age at the skeletal age assessment; negative values represent more delayed skeletal maturity (chronological age $>$ skeletal age), and positive values represent more advanced skeletal maturity (chronological age $<$ skeletal age).

Table II

skeletal maturity at age 9 years in 467 white children in the Fels Longitudinal Study and 196 South African black children in the Birth to 21 Study. Parameter estimates (standard errors) from multivariate linear regression models

	Model 1			Model 2			Model 3			Model 4		
	Fels	P	Bt20	P	Fels	P	Fels	P	Bt20	P	Fels	P
Age at skeletal maturity (years)	0.16 (0.10)	.10	0.34 (0.12)	.005	0.23 (0.10)	.022	0.45 (0.12)	<.0001	0.20 (0.10)	.037	0.40 (0.12)	.001
Sex (male)	0.04 (0.04)	.24	-0.02 (0.04)	.706	0.01 (0.04)	.70	-0.08 (0.04)	.066	0.05 (0.04)	.18	-0.08 (0.04)	.056
Parity	0.01 (0.003)	.025	-	-	0.01 (0.003)	.014	-	-	0.002 (0.003)	.34	-	-
Birth weight (kg)	0.21 (0.009)	<.0001	0.16 (0.06)	.004	0.29 (0.05)	<.0001	0.28 (0.06)	<.0001	0.18 (0.05)	.005	0.20 (0.07)	.003
Birth length (cm)	-	-	-	-	0.18 (0.07)	.006	0.32 (0.08)	<.0001	0.01 (0.07)	.91	0.23 (0.08)	.006
Birth weight (kg) squared	-	-	-	-	-	-	-	-	0.38 (0.05)	<.0001	0.17 (0.06)	.007
Birth length (cm) squared	-	-	-	-	-	-	-	-	-	-	0.52 (0.05)	<.0001
Constant	0.043		0.077		0.057		0.149		0.161		0.316	
									0.177		0.285	

for sex, gestational age, maternal age, parity, birth year (FLS only), and weight gain 0 to 2 years.

for sex, gestational age, maternal age, parity, birth year (FLS only), weight gain 0 to 2 years, and birth weight.

for sex, gestational age, maternal age, parity, birth year (FLS only), weight gain 0 to 2 years, birth weight, and BMI at age 9 years.

for sex, gestational age, maternal age, parity, birth year (FLS only), weight gain 0 to 2 years, birth weight, BMI at age 9, and height at year 9.