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Birth characteristics and age at menarche: results from the dietary intervention study in children (DISC)

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Abstract

Objective—To examine whether birth weight, birth length, and gestational age are individually associated with age at menarche.

Methods—Analyses were conducted using data from $n = 278$ female participants in the Dietary Intervention Study in Children (DISC). Age at menarche was prospectively collected as part of the original DISC investigation. DISC participants self-reported birth weight, birth length, and gestational age with assistance from their mothers and other records as part of the DISC06 Follow-up Study at ages 25–29. Linear regression was used to estimate the association of birth characteristics and age at menarche.

Results—Birth weight was positively associated with age at menarche ($p \leq 0.01$) in multiple regression analyses after controlling for BMI-for-age percentile, race and DISC treatment group. No statistically significant relationships were detected between either length or gestational age and age at menarche.

Conclusions—Higher birth weight may be associated with a modest delay in age at menarche.

Keywords

Menarche; Birth weight; Birth length; Gestational age; Puberty; Breast cancer

Introduction

Age at menarche (first menses) has declined in the United States and internationally [1–3]. In addition to the short-term risks associated with early pubertal maturation, including increased risk of adolescent substance abuse, phycological distress and early sexual intimacy [4–6], earlier age at menarche is a documented risk factor for breast cancer [7–9]. Endogenous estradiol concentration peaks with ovulation; thus the more ovulatory menstrual

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cycles a woman experiences, the greater her lifetime exposure to estradiol. Earlier menarche is associated with an increased number of ovulatory menstrual cycles [10, 11] and accordingly, this is one suspected mechanistic pathway linking early menarche to increased breast cancer risk.

A growing body of literature has documented a positive association between birth weight and breast cancer, with the evidence being stronger for pre-menopausal cancer [12, 13]. Much of this literature is framed in the context of the four assumptions of Trichopolous' fetal origins of breast cancer hypothesis: (1) estrogens are an important component in breast carcinogenesis, (2) factors that increase the risk of cancer post-natally may also increase the risk of cancer when they act in utero, (3) estrogen concentrations are at least ten times higher during pregnancy than they are during other periods in adult life, (4) estrogen concentration and secretion rates vary widely between individuals during pregnancy, and this variability is partly accounted for by exogenous factors [14].

The positive associations between maternal circulating estrogens during pregnancy and offspring birth weight [15–17] have led some to hypothesize that increased birth weight is a marker for increased fetal estrogen exposure. However, the correlation for estrogen concentrations in the fetal and maternal compartments appears to be low [18–20], suggesting maternal circulating estrogens are not an appropriate proxy for fetal exposure and alternative mechanisms may be at play. Substantially, less work has examined birth weight and intermediary risk factors, such as age at menarche; although such work could offers insight into the mechanism by which birth weight and breast cancer risk are associated. The limited work that has been published suggests that birth weight is positively related to age at menarche [21–23], but that this relationship may be mediated by rapid increases in growth (also referred to as growth velocity) from two to seven years of age [24]. The positive association of birth weight and age at menarche has also been documented among girls experiencing precocious puberties [25]. Studies which examine birth length or gestational age and age at menarche are limited [24, 26, 27], although a positive association between birth length and breast cancer risk and an inverse relationship between gestational age and breast cancer risk have been documented [13].

The relationship between birth characteristics and age at menarche deserves further attention in order to clarify the association of breast cancer risk factors over the life course. To that end, we assessed the relationship between birth weight, birth length, and gestational age with age at menarche after controlling for potential covariates such as physical activity, body mass index, and mother's age at menarche in the Dietary Intervention Study in Children (DISC) [28]. Based on the previous literature, we hypothesized that birth weight and birth length would be positively and gestational age would be inversely associated with age at menarche.

Subjects and methods

The present investigation analyzed data from female participants in the original DISC (conducted 1988–1997) with data supplemented from the DISC Follow-up Study (conducted 2006–2008, hereafter referred to as DISC06). Briefly, the original DISC investigation was a two-armed, multi-center, randomized clinical trial sponsored by the National Heart Lung and Blood Institute (NHLBI) to assess the safety and efficacy of a reduced fat dietary intervention during adolescence on serum cholesterol and serum hormones for evaluation at six clinical centers [29]. Details of the dietary intervention strategy have been published [30]. The purpose of the DISC06 was to evaluate female DISC participants in early adulthood (ages 25–29) for potential effects of the DISC intervention during puberty on biomarkers associated with breast cancer risk. Institutional Review Boards at all participating centers approved both DISC protocols, and an NHLBI-appointed independent data and safety monitoring committee provided oversight for the original DISC investigation.

Data for the original DISC investigation were collected prior to randomization and annually thereafter by trained staff who were blinded to treatment assignment. Demographic characteristics, medical history, physical activity, and use of medications were obtained via self-report with parental assistance where necessary in the original DISC investigation. Measures of weight, height, and body mass index (BMI: weight in kg/height in m^2) were obtained using standardized techniques previously described [30]. Information on weight and height prior to DISC enrollment was not available. Mother's age at menarche was reported (in whole years) by $n = 163$ mothers accompanying their daughters to the Year-3 visit as part of a parent/guardian questionnaire.

Onset of participant menses was reported in the original DISC to the nearest day and ascertained annually until menarche was reached or the conclusion of the original DISC investigation. When the exact date was unknown, the date was imputed as the 15th of the month. Age at menarche was also ascertained in self-reported questionnaire as part of the DISC06 (collected in whole years). For the present analysis, there were $n = 34$ individuals for whom age at menarche was not reported in the original DISC investigation, but who did report age at menarche in DISC06. Our final sample for menarche data was comprised of 250 individuals from the original data collection plus the 34 individuals who reported age at menarche only in the follow-up study (total $n = 284$). For the individuals who reported age at menarche in the DISC06 (in whole years) and also reported age at menarche recorded in the original DISC investigation, the mean difference between the originally recorded and retrospectively recalled age at menarche was +0.27 years (95% confidence interval (CI): 0.11–0.44), thus suggesting accurate recalled age at menarche.

Birth weight was recorded to the nearest ounce or gram as part of the mothers'/guardians' questionnaire for the Year-3 visit of the original DISC investigation. A total of $n = 203$ (67.4%) participants had a reported birth weight as part of the Year-3 visit, but it was unknown whether the report was made by the participants' mothers or another adult accompanying the child to the visit. To capture more complete birth characteristics data, birth weight, in addition to birth length and gestational age were obtained as part of DISC06. The young women were sent a birth characteristics questionnaire by mail prior to their clinic visit and asked to consult their birth certificates, records, and family members in order to provide an accurate report. The questionnaire ascertained birth weight (pounds, ounces), birth length (to the nearest tenth of an inch), gestational age (in weeks), and whether the pregnancy was full term (specified as ≥37 weeks). Two hundred and sixty women participated in the DISC06, and response rates for the birth characteristics were high (99.6% for birth weight, 94.2% for birth length, 75.0% for gestational age in weeks, and 99.6% for whether the birth was term (Y/N). Women could report one or more source(s) for birth characteristics; 87% ($n = 226$) reported asking their mothers, 57% ($n = 149$) reported themselves as the source of information, 14% ($n = 37$) reported using a baby book, 14% ($n = 37$) reported consulting other people or other records, and 9% ($n = 24$) reported consulting their birth certificate. For the birth weight analyses, a sample of 282 individuals was used (comprised of the 259 birth weights collected from the follow-up study and supplemented by 23 individuals who reported birth weight only in the original DISC data collection), of these $n = 278$ had a reported age at menarche. The Pearson correlation coefficient for birth weight among the 180 women with a recorded birth weight during the original DISC investigation at the 2006–2008 follow-up study was 0.87 ($p<0.0001$, mean difference = −5.65 g, 95% confidence interval (CI): −42.39–31.07 g, minimum absolute difference: 0.007 g, maximum absolute difference: 1,219 g).

Statistical analysis

Statistical analyses were performed using SAS software (SAS System for Windows, version 9.1; SAS Institute, Cary, NC). BMI-for-age percentiles were calculated using the U.S. Centers for Disease Control SAS Program for Growth Charts [31]. One-way ANOVA analyses were used to compare differences in mean birth weight, birth length, gestational age, BMI-for-age percentile at the visit prior to reaching menarche, MET score at the visit prior to reaching menarche, and mother's age at menarche between early (≤11.75 years), average (11.76–13.74 years), and late menarche (≥13.75 years) groups. These categories are based roughly on the mean age at menarche ± one SD.

Birth characteristics (birth weight, birth length, gestational age) were treated as predictor variables with age at menarche in years as the dependent variable in linear regression models. Overall, birth weight was highly positively correlated with birth length ($r = 0.49$, $p<0.0001$) and birth length was positively correlated with gestational age ($r = 0.20$, $p = 0.005$). For this reason, separate multivariable analyses were performed with each of these covariates.

We modeled the birth characteristics (birth weight, birth length, and gestational age) in two ways to assess the shape of the relationship between birth characteristics and age at menarche. First, participants were divided into quartile of birth weight, birth length, or gestational age to quantify the association of membership in a specific quartile and age at menarche compared with that in the highest quartile. Tests for linear trend were conducted using the median value of the birth characteristic in each category as a continuous variable. The sample sizes for birth weight, birth length, and gestational age for analyses with complete covariates were $n = 273$, 242, and 193, respectively. Second, we modeled birth weight, birth length, or gestational age as a continuous variable to achieve maximal statistical power. Mother's age at menarche was available for a subset of the girls (163/278 girls with birth weight and age at menarche data, 161/278 with complete covariates). Thus, a sub-analysis was performed with data for $n = 161$ girls to assess the association and evaluate potential confounding by the mother's age at menarche in addition to the previously specified independent variables.

To build the model, we began by including the *a priori* variables of intervention group and race and individually added birth weight, birth length, gestational age (as continuous variables), term birth (yes/no), BMI-for-age percentile, and other covariates in separate models. If the variable was significant at the $p \leq 0.05$ level in the model containing the *a priori* variables, it was added to the final model via one addition at a time. The following potential covariates were examined but did not have statistically significant effect (defined as $p<0.05$) in the model including treatment and race and thus were not included in the final model: MET score, MET score of moderate-intense physical activity, percent energy from fat, total fat, total energy divided by body weight, and pondered index at birth. All time varying covariates were examined at the visit prior to reaching menarche. Cigarette smoking prior to menarche was only reported by two individuals and was not included in the analysis.

Results

The mean age at menarche for the $n = 278$ girls with both reported birth weight and age at menarche was 12.89 years with a standard deviation (SD) of 1.20 years (range 9.75–17.31 years). Twenty-nine girls (10.4%) reported clinical low birth weight (≤2,500 g at birth) and twenty-seven girls (9.7%) reported weighing ≥4,000 g at birth. As previously reported, menarche and Tanner stage progression did not differ at any visit by DISC intervention group [32]. Results from unadjusted one-way ANOVA analyses to compare differences in mean birth weight, birth length, gestational age, BMI-for-age percentile, MET score, and mother's age at menarche between early (≤11.75 years), average (11.76–13.74 years), and late-menarche (≥13.75 years) groups are shown in Table 1. Mean birth weight increased with age at menarche categorization (early, average, or late), but the unadjusted between group differences in birth weight were not statistically significant at $p \le 0.05$, nor was there a statistically significant overall *p*-value. No differences in mean birth length, mean gestational age, or mean physical activity (measured as MET score) were detected across the age at menarche groups. Significant overall mean group differences were detected by age at menarche group for BMI-for-age percentile at the visit directly before reaching menarche ($p<0.0001$,). Among the 163/278 girls (59% of the sample) with reported birth weight, age at menarche and mother's age at menarche; girls with early menarche also had the earliest reported mean mother's age at menarche. The differences in group means for mother's age at menarche by daughter's age at menarche were statistically significant ($p \le 0.006$, with a difference of approximately 0.73 years in mother's age at menarche among early vs. average menarche groups, 0.41 years among average vs. late menarche groups, and 1.14 years among early vs. late menarche groups).

Linear regression analyses of the full sample indicated a positive relationship between birth weight and age at menarche. In the unadjusted test for trend analyses, both quartile of birth weight and birth weight modeled as a continuous variable were positively associated with age at menarche (quartile *p*-trend<0.01, continuous birth weight $p<0.01$). No significant interaction between quartile of birth weight and covariates, including BMI-for-age percentile was detected ($p = 0.18$). Following covariate adjustment, women belonging to the lowest quartile of birth weight experienced menarche 0.51 years (~6 months) earlier compared to women in the highest quartile of birth weight (95% CI: −0.88, −0.14; $p<0.01$, *p*-trend<0.01). Modeling birth weight as a continuous variable with covariate adjustment also indicated that the adjusted birth weight effect was statistically significant ($p<0.01$) with each 500 g increase in birth weight associated with a 0.21 year (approximately 2.7 month) delay in age at menarche. Birth weight was not associated with BMI-for-age percentile prior to menarche ($p = 0.39$).

The association between birth length and age at menarche was not statistically significant when birth length was modeled in quartiles or as a continuous variable in either the unadjusted or adjusted tests for trend. In addition, the association between gestational age and age at menarche was not statistically significant when modeled in either the unadjusted or adjusted models as either quartiles of gestational age or as a continuous variable. No significant association was detected between full-term birth and age at menarche.

A sub-sample with data on birth weight, mother's age at menarche and complete covariates was available for $n = 161$ study participants (Table 2). Unadjusted trend analysis of the sub-sample indicated an association of birth weight as a continuous variable and age at menarche in the same direction of the full model, but the unadjusted association was not statistically significant. Excluding mother's age at menarche but adjusting for other characteristics (DISC intervention group, race, and BMI-for-age percentile) in the $n = 161$ sub-sample indicated a null relationship of birth weight and age at menarche ($\beta = 0.14$, 95% CI: −0.05, 0.32, $p = 0.14$; data not shown). Given that adjusted birth weight in the $n = 278$, sample was significant at $p \le 0.01$ suggests that the sub-sample size of $n = 161$ was inadequate to detect an effect of birth weight, even without including mother's age at menarche as a covariate. The addition of mother's age at menarche to the model indicated a strong positive association between mother's age at menarche and daughter's age at menarche ($p = 0.0004$), but as expected based on the unadjusted analyses, birth weight was not statistically significant likely due to inadequate sample size. The fully adjusted regression of quartile of birth weight on mother's age at menarche was null (Q1 vs. Q4: −0.36; 95% CI: −0.85, 0.12

p-trend = 0.24, Model 1) as was birth weight modeled as a continuous variable (estimate = 0.14, 95% CI: −0.04, 0.32, *p* = 0.13; Model 2).

Discussion

In this study, we found that birth weight was positively associated with age at menarche, independent of DISC intervention group, race and recent BMI-for-age percentile. Results from our birth weight analysis support those of the Medical Research Council (MRC) National Survey of Health and Development Birth Cohort 1946 [33]. In that study, height and weight at age 7 years were recorded by school health workers. The girls' age at menarche was ascertained when the participants were 14.5 years old by asking their mothers the month and year onset of menses occurred. Results indicated that the group with the youngest age at menarche (mean = 11.89 years) had the lowest birth weight (<2,850 g) and were heaviest (>24.9 kg) at 7 years. Including birth weight, height and weight at age 7 simultaneously in a survival model suggested that both birth weight ($p<0.0001$) and weight at age 7 years ($p<0.0001$) were significantly associated with age at menarche. The study did not investigate mother's age at menarche or physical activity. Later analyses of the same cohort [24] initially suggested that lower birth weight was associated with earlier age at menarche, but the association with birth weight, as well as the effect of growth velocity (defined as change in rank order) between birth and 2 years of age, disappeared when growth velocity from 2 to 7 years was included in the model. This suggests that the effect of early life characteristics on timing of menarche is mediated through childhood growth from 2 to 7 years of age [24]. If such an effect is true, it helps to explain why lower birth weight is associated with earlier age at menarche yet high birth weight is associated with increased breast cancer risk. Annual height and weight measurements between birth and study entry were not available in the DISC cohort, but if accessible would have allowed us to quantify growth velocity and possibly refine our results.

Few studies have investigated the associations of birth length and gestational age with age at menarche. The combination of being born long in length and light in weight has been associated with earlier age at menarche in two studies [26, 34], suggesting that third trimester in utero energy depravation may potentially influence neuroendocrine development. We are not aware of any studies that document a statistically significant independent effect of either birth length or gestational age with age at menarche although an earlier age at menarche has been documented among girls born small-for-gestational age [22, 35, 36]. Our results are similar to those of recent analyses of $n = 262$ racially diverse participants in the US National Collaborative Perinatal Project which found no statistically significant association of birth length or gestational age (as assessed by assessed by trained clinical researchers in the perinatal period) with self-reported age at menarche (during ages 38–46 years) after adjusting for birth weight and other covariates [27].

Although the body of evidence linking birth weight and many chronic diseases is robust, knowledge of the specific biological mechanisms influencing prenatal programming is nascent. Research must continue to explore alternate explanations aside from birth weight as a proxy for in utero estrogen exposure to explain the association between birth weight, and breast cancer risk. In particular, greater attention is needed on the potential effects of androgen exposure in utero. Fetal androgens are involved in imprinting the hypothalamus for the pulsatile control of gonadotropin-releasing hormone (GnRH) which is responsible for the onset of puberty [37, 38]. It is speculated that in utero androgen exposure may offer breast cancer protection by antagonizing the effects of estrogens on ductal development in the fetal breast [39]. Birth size has been inversely associated with androgen production in childhood and adolescence [40–42], suggesting that early life characteristics may have long reaching effects on serum hormones. The interplay of the effect of birth characteristics, pubertal development, and future breast cancer risk deserves further attention and future investigations of the DISC Girls will examine the association of birth characteristics with concentrations of serum sex hormones during adolescence. A recent study of steroid hormone concentration in Chinese and U.S. Caucasian neonates found that after multivariate adjustment, Chinese infants had significantly higher androstenedione (60.5%) and testosterone (185%) compared to U.S. Caucasian infants [43]. These data may help explain the lower breast cancer incidence rates in Asians not explained by adult risk factors. In addition, Asian-Americans and well-nourished Chinese have been reported to have a relatively early menarche compared to U.S. Caucasians, despite lower average fat mass in early adolescence [44–46].

Several limitations of the present study should be addressed in future studies. Data on mother's age at menarche were available for 163 participants, but the statistical power to detect an effect of birth weight in this sub-sample was limited. The original DISC lacked data on height and weight between birth and study entry. Thus, we were not unable to quantify early childhood growth velocity; nor were data available on maternal characteristics during the index pregnancy such as presence of preeclampsia, gestational diabetes, or tobacco use. However, given the size of our study sample, the prevalence of preeclampsia and gestational diabetes were likely low. Other limitations of the present investigation include self-reported birth characteristics that may have been subject to error. However, most DISC participants asked their mothers for information on their birth characteristics and maternal report of birth characteristics are highly correlated with birth characteristics in the medical record, although birth weight is more accurately recalled than other birth characteristics [13, 47, 48]. In addition, participants had elevated LDL-C at baseline and eligibility was restricted to those ≥5th percentile for height and in the 5–90th percentiles for weight-for-height which may limit generalizability.

Strengths of our study include the availability of prospectively collected measurements beginning at study entry, including detailed information on timing of menarche, measured height and weight prior to and during puberty, and the availability of mother's age at menarche for a subset of study population. Although our sample lacks racial/ethnic diversity, previous research has suggested that perinatal characteristics as surrogates for hormone levels should be limited to a specific ethnic group due to significant variation in effect [49], and hence the racial homogeneity of our sample is a strength.

In summary, findings from DISC suggest that increased birth weight is associated with later age at menarche. Future work should aim to clarify the role of growth velocity (including height, weight, and BMI velocity) during specific ages of childhood. Additional work is needed to determine whether birth characteristics (e.g. birth weight) are suitable proxy measures for fetal hormones exposure.

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Table 1

Study characteristics of DISC girls with early, average, or late Menarche

	Overall Mean(SD) ***n*** **Range**	**Early (≤11.75 years) Mean (SD)** ***n***	**Average (11.76–13.74 years) Mean (SD)** ***n***	**Late (≥13.75 years) Mean (SD)** ***n***	**Between group *p*-value**	**Overall *p*-value**
Birth weight (g)	3411.33 (496.39) *278*	3298.47 (496.89) *40*	3411.39 (479.61) *186*	3497.90 (545.38) *52*	0.19† 0.27‡ 0.06§	0.16
Birth length (cm)	51.12 (2.80) *242* 40.64–57.15	50.76 (3.00) *36*	51.06 (2.68) *158*	51.59 (3.01) *48*	0.57† 0.25‡ 0.18§	0.36
Gestational age (weeks)	38.72 (2.28) *193* 24.0–43.0	38.93 (2.25) *27*	38.87 (2.03) *122*	38.18 (2.86) *44*	0.91† 0.09‡ 0.18§	0.20
BMI-for-age percentile at visit prior to menarche*	28.13 (28.52) *273* 0.89–98.49	71.87 (19.70) *40*	59.04 (27.46) *182*	44.11 (32.25) *51*	<0.01† <0.001‡ <0.0001§	<0.0001
METs at visit prior to menarche	277.5 (43.90) *265* 22.50–467.25	277.64 (52.06) *40*	265.38 (41.21) *176*	286.26 (45.92) *49*	<0.76† <0.17‡ <0.44§	0.39
Mean mother's age at Menarche (Year)	12.91 (1.34) *163* 10.0–19.0	12.21 (1.32) *24*	12.94 (1.28) *108*	13.35 (1.40) *31*	0.02† 0.12‡ <0.01§	0.006
Race						
White	*236*	*24*	*167*	*45*		
Black	*15*	*3*	*10*	*2*		
Asian	*11*	*7*	*4*	*0*		
Not reported	*16*	*6*	*5*	*5*		

SD = standard deviation

n of each cell varies due to missing data

* mean age at last visit prior to menarche = 11.75 years, SD = 1.31, range 8.34 –16.30 years

† comparing early to average

‡ comparing average to late

§ comparing early to late

Table 2

Unadjusted and adjusted results from multiple linear regression of daughter's age at Menarche on birth weight, adjusted for mother's age at Menarche

Characteristics	Unadjusted Regression Coefficient	Unadjusted 95% CI	Unadjusted *p*-value	Adjusted* Regression Coefficient	Adjusted* 95% CI	Adjusted* *p*-value
Model 1[a]						
Birth weight (g)						
Q1 (≤3,175)	−0.52	−1.07, 0.03	0.07	−0.38	−0.87, 0.11	0.13
Q2 (3,176–3,487)	−0.44	−0.97, 0.08	0.09	−0.35	−0.82, 0.12	0.15
Q3 (3,588–3,714)	−0.59	−1.16, 0.02	0.04	−0.55	−1.07, −0.04	0.04
Q4[†](≥3,715)	–	–	–	–	–	–
Trend test	<0.01	0.00, <0.01	0.12	<0.01	0.00, <0.01	0.24
Intervention group race	−0.06	−0.45, 0.33	0.77	−0.06	−0.40, 0.28	0.73
White[†]	–	–	–	–	–	–
Black	−0.03	−0.78, 0.73	0.95	−0.25	−0.93, 0.44	0.48
Asian	−1.57	−2.67, −0.48	<0.01	−1.80	−2.79, −0.81	<0.001
Not reported	−0.69	−1.91, 0.53	0.27	−0.43	−1.54, 0.67	0.44
BMI-for-age percentile[‡]	−0.16	−0.22, −0.10	<0.0001	−0.13	−0.19, −0.07	<0.0001
Mother's age at Menarche(y)	0.28	0.14, 0.42	0.0001	0.25	0.12, 0.38	<0.001
Model 2 [a]						
Birth weight[§]	0.20	−0.01, 0.40	0.06	0.14	−0.04, 0.32	0.13
Intervention group	−0.06	−0.45, 0.33	0.77	−0.05	7.50, 11.93	0.77
Race						
White[†]	–	–	–	–	–	–
Black	−0.03	−0.78, 0.72	0.95	−0.16	−0.83, 0.52	0.65
Asian	−1.57	−2.67, −0.78	<0.01	−1.70	−2.69, −0.71	<0.001
Not reported	−0.69	−1.91, 0.53	0.27	−0.51	−1.60, 0.58	0.36
BMI-for-age percentile[‡]	0.28	0.14, 0.42	0.0001	−0.13	−0.19, −0.07	<0.0001
Mother's age at Menarche (years)	−0.16	−0.22, −0.10	<0.0001	0.24	0.11, 0.37	<0.001

[a] *Model 1* examines quartiles of birth weight, *Model 2* examines birth weight as a continuous variable

* adjusted for characteristics in table, based on *n* = 161 participants with complete data

† reference

‡ per 10-point increase

§ per 500 gram increase