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ORIGINAL ARTICLES

Post-Term Birth is Associated with Greater Risk of Obesity in Adolescent Males

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Objective To test the hypothesise that post-term birth (>42 weeks gestation) adversely affects longitudinal growth and weight gain throughout childhood.

Study design A total of 525 children (including 17 boys and 20 girls born post-term) were followed from birth to age 16 years. Weight and height were recorded prospectively throughout childhood, and respective velocities from birth to end of puberty were calculated using a mathematical model.

Results At birth, post-term girls were slimmer than term girls (ponderal index, 27.7 ± 2.6 kg/m^3 vs 26.3 ± 2.8 kg/m^3; $P < .05$). At age 16 years, post-term boys were 11.8 kg heavier than term subjects (body mass index [BMI], 25.4 ± 5.5 kg/m^2 vs 21.7 ± 3.1 kg/m^2; $P < .01$). The rate of obesity was 29% in post-term boys and 7% in term boys ($P < .01$), and the combined rate of overweight and obesity was 47% in post-term boys and 13% in term boys ($P < .01$). Weight velocity, but not height velocity, was higher in post-term boys at age 1.5-7 years ($P < .05$) and again at age 11.5-16 years ($P < .05$). BMI was higher in post-term boys at age 3 years, with the difference increasing thereafter. BMI and growth were similar in post-term and term girls.

Conclusion In this post-term birth cohort, boys, but not girls, demonstrated accelerated weight gain during childhood, leading to greater risk of obesity in adolescence. *(J Pediatr 2011;■:■-■).*

Obesity is a major risk factor for various chronic diseases in adults,[1] and its prevalence has dramatically increased in many developed countries over the past 20 years, especially among children.[2] Although some earlier epidemiologic studies examined childhood and adult risk factors, recent longitudinal studies have highlighted the crucial role of early life events, including those occurring before birth.

Small size at birth is associated with a variety of adult diseases, including type 2 diabetes, ischemic heart disease, and obesity.[3] Individuals who were born preterm appear to be more prone to insulin resistance.[4,5] Furthermore, rapid weight gain during infancy and childhood in low birth weight (LBW) and preterm subjects has been identified as a major contributing factor to the development of obesity and insulin resistance, as well as to adult metabolic and cardiovascular diseases.[6-8] Preterm birth is also associated with considerable mortality and long-term morbidity.[9,10]

In contrast, post-term birth (at >42 completed weeks of gestation or >293 days from the first day of the last menstrual period)[11] has no known associated long-term sequelae, but it has been linked to greater perinatal mortality and morbidity.[12,13] A large number of children worldwide are born post-term, with estimates as high as 8.1% of all live births in Europe[14] and approximately 5.6% in the United States.[15] Studies of LBW and preterm subjects suggest discrete periods in which programmed changes can occur leading to later adult disease. However, although there are limited data suggesting adverse neurologic/developmental outcomes associated with post-term birth,[16] the growth and metabolism of post-term children have not yet been studied. Nonetheless, it is known that prolonged gestation may lead to a suboptimal fetal environment through inadequate nutrition or physiological stress, resulting in long-term postnatal alterations in body composition. Consequently, we aimed to determine whether post-term birth affects longitudinal weight gain throughout childhood and adolescence, and whether it affects the likelihood of developing obesity in adolescence.

Methods

This study involved an initial cohort recruited from birth comprising 764 girls and 712 boys, recruited from the Swedish Medical Birth Registry. All subjects were born in Göteborg, Sweden between October 1980 and June 1986. All subjects had growth measured longitudinally between birth and age 14-18 years. All those who were born at >37 weeks of gestation and had anthropometric data recorded at age 16 years were included in this analysis. The subjects were divided into 2

BMI	Body mass index
LBW	Low birth weight

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groups according to gestational age at birth: term (37-42 weeks gestation) and post-term (>42 weeks gestation). Gestational age was determined by hierarchical integration of the following variables: date of last menstrual period, menstrual cycle length, ultrasound primarily at 16-20 weeks, and clinical assessment of gestational age at birth.[17,18] The incidence of post-term delivery in this cohort is similar to that reported in the literature,[19] indicating that the estimated gestational age at birth is not significantly biased.

To evaluate for an association between post-term birth and changes in weight and/or height gain, mathematical models for height and weight velocities (from birth to the end of puberty) were developed. Ordinary differential equations for height and weight dynamics were solved using MATLAB version 7.10 (MathWorks, Natick, Massachusetts). The model was parameterized separately for each subject.

The first time point used to compare auxologic data was birth. Children were measured between 3 and 5 times a year from birth to 3 years, and then yearly until the end of the study. The final measurement was made between 16 and 17 years. Auxologic data were analyzed separately for males and females using the parametric Student *t*-test or the nonparametric Wilcoxon rank-sum test. The effects of term or post-term birth and birth weight (or ponderal index) on auxologic data (height, weight, and body mass index [BMI]) were evaluated at birth and 16 years using multivariate linear regression models, with actual age at measurement included in as a covariate. Values of height velocity, weight velocity, weight, height, and BMI calculated with the mathematical model during all growth periods were compared in the term and post-term groups using parametric and nonparametric tests. Overweight and obesity were defined according to the Swedish chart for boys and girls,[20] and the incidence of obesity and overweight was compared between groups using the Fisher exact test. Data were analyzed using R version 2.9.0 (R Foundation for Statistical Computing, Vienna, Austria). Data are presented as mean ± SD.

The study was approved by the Ethics Committee at the Sahlgrenska Academy at Göteborg University and by the Swedish Data Authorities. Written informed consent was obtained from all participants and/or their parents.

Results

A total of 250 boys and 275 girls met the criteria and were included in this study, of which 17 boys (7.1%) and 20 girls

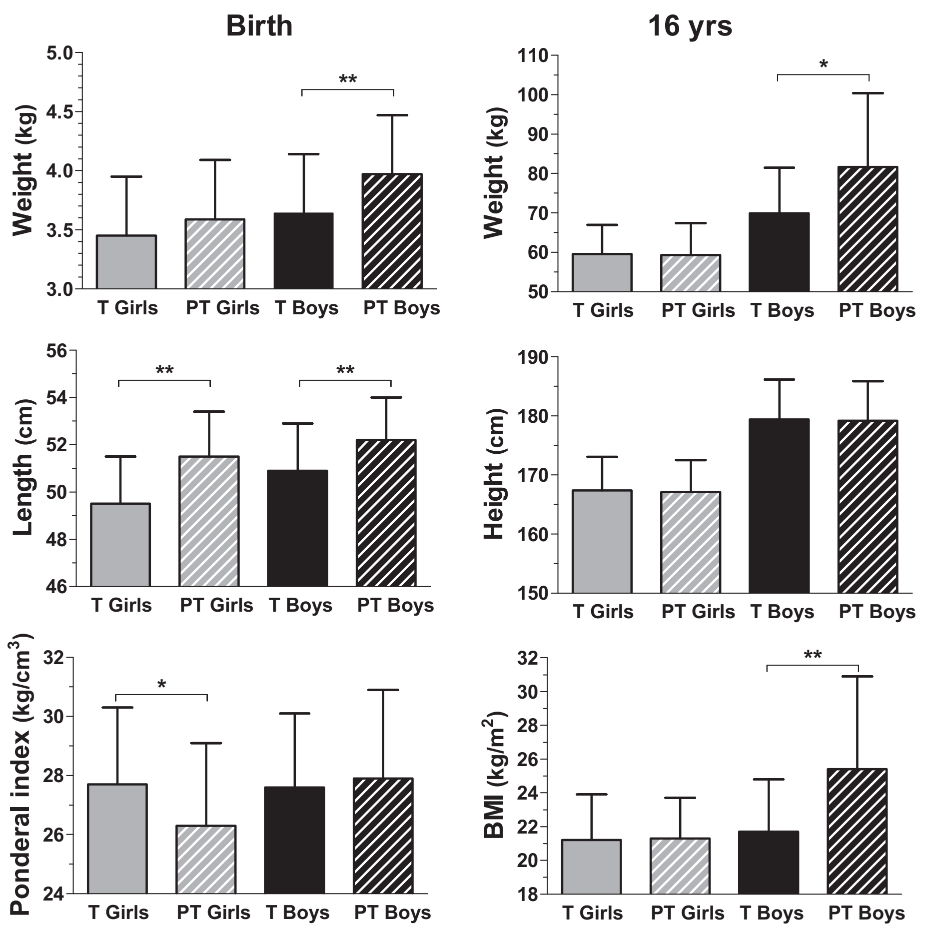

Figure 1. Auxologic data at birth and age 16 years. *T*, term; *PT*, post-term. Data are mean ± SD. *$P < .05$; **$P < .01$ for term versus post-term comparisons.

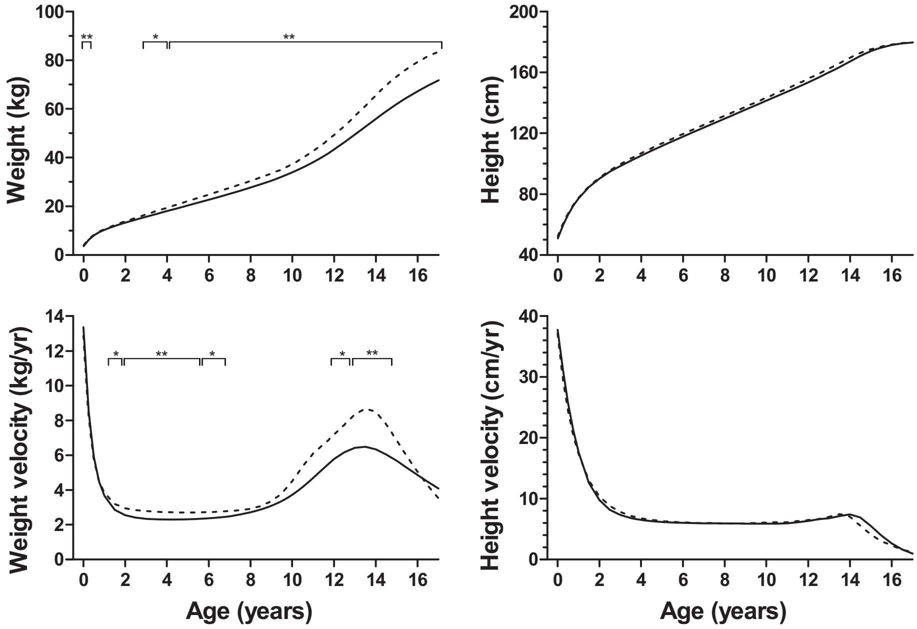

Figure 2. Weight, height, and respective velocity data for term (*solid line*) and post-term (*dashed line*) boys from birth to age 17 years. Data are means. *$P < .05$; **$P < .01$ for term versus post-term comparisons.

(6.5%) were born post-term. Twenty-six measurements were recorded per subject. Birth weight was similar in post-term girls and term girls, whereas post-term girls were longer (51.5 ± 1.9 cm vs 49.5 ± 2.0 cm; $P < .01$) and had a lower ponderal index (26.3 ± 2.8 kg/cm^3 vs 27.7 ± 2.6 kg/cm^3; $P < .05$) (Figure 1). Post-term boys were heavier (3.97 ± 0.5 kg vs 3.64 ± 0.5 kg; $P < .01$) and longer (52.5 ± 1.8 cm vs 50.9 ± 2.0 cm; $P < .01$) than term boys at birth, although the ponderal index was similar in the 2 groups (Figure 1).

There were clear differences in weight gain patterns between post-term boys and girls. Post-term boys had 2 periods of rapid weight gain, at age 1.5-7.0 years and 11.5-16.0 years (Figure 2). Weight and height were similar in post-term and term boys after birth as soon as 1.5 and 9 weeks of life, respectively, but subsequent weight velocity changes resulted in divergent mean weight curves (Figure 2). The rapid weight gain in post-term boys was associated with higher BMI as early as age 3 years (Figure 3). Conversely, there were no differences in weight gain throughout childhood between post-term and term girls (data not shown). Further, height velocity throughout childhood did not differ between post-term boys (Figure 2) and girls (data not shown) and their term counterparts. However, the pubertal growth spurt began at an earlier age in post-term boys than in term boys (12.5 ± 2.0 years vs 13.5 ± 1.4 years; $P < .01$).

At age 16 years, the post-term and term groups were of similar height, but post-term boys were approximately 11.8 kg heavier ($P < .05$) and had a 3.7-kg/m^2 greater BMI ($P < .01$) than term boys (Figure 1). The rate of obesity (BMI >95th percentile for age) was 29% in post-term boys and 7% of term boys ($P < .01$). The BMI differences were even more marked when the prevalence of obese and overweight (BMI >85th percentile for age) boys were combined, with rates of 47% in post-term boys and 13% in term boys ($P < .01$). In contrast, weight, height, and BMI were similar in term girls and post-term girls (Figure 1). Notably, mid-parental BMI was similar in post-term boys and post-term girls (25.7 ± 0.9 kg/m^2 vs 25.2 ± 0.9 kg/m^2; $P = .56$).

Across both post-term and term subjects, boys and girls who were longer at birth were also taller at age 16 years ($\beta = 1.25$ cm; $P < .001$ vs $\beta = 0.75$; $P < .001$). Among boys,

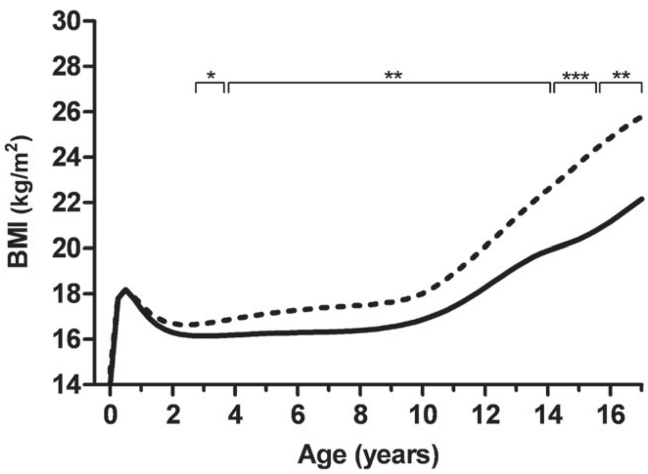

Figure 3. BMI data for term (*solid line*) and post-term (*dashed line*) boys from birth to age 17 years. Data are means. *$P < .05$; **$P < .01$; ***$P < .001$ for term versus post-term comparisons.

post-term birth, but not birth weight, was associated with increased BMI at age 16 years ($\beta = 1.85$ kg/m^2; $P < .001$).

Discussion

The present study provides evidence of a likely association between post-term birth and negative long-term health outcomes in boys. Programmed metabolic changes in childhood and adult life are known to be associated with preterm birth and LBW. However, the magnitude of weight gain in these groups is far less than that seen in adolescent post-term males. Although prematurity and LBW are known to be associated with adiposity in later adult life, these infants are lean and/or small at birth, whereas post-term males are not. Most importantly, post-term boys displayed accelerated weight velocity and subsequent obesity decades earlier than has been reported in LBW or preterm boys. This increased weight velocity was associated with a dramatically higher incidence of overweight and obesity after puberty, with almost half of the post-term boys overweight and/or obese at age 16 years. Given the progressive weight gain observed throughout adult life in persons born with LBW or born preterm, it is conceivable that the post-term males that we studied are likely to develop even greater adiposity in adult life; thus, this group would be at an even greater risk of developing obesity-related diseases, such as type 2 diabetes mellitus, hypertension, and dyslipidemia.

There were clear sex-dependent differences among post-term subjects. At birth, girls were leaner than boys, and boys exhibited accelerated weight gain early in childhood and again at puberty, resulting in greater adiposity and obesity that was not seen in girls. Although slightly thinner than their term counterparts, post-term girls were not small for gestational age and might have sustained only minimal intrauterine growth restriction that did not constrain later growth. Sexual dimorphism also has been noted in other groups exposed to an altered early life environment, such as those conceived after in vitro fertilization.[21,22] The exact mechanisms underpinning the observed sex differences are unclear, but these differences may be associated with a greater capacity of post-term males to maintain body weight during nutritional compromise or a different adaptive response to physiological stress. Thus, in post-term males, a thrifty phenotype with greater nutritional and metabolic efficiency may lead to a propensity toward adiposity when calorie intake is unrestricted in postnatal life.

Maternal obesity slightly increases the likelihood of post-term birth,[23,24] and higher parental BMI has been reported to be associated with obesity in childhood.[25] However, there was no difference in mid-parental BMI between post-term boys and girls in our cohort, and thus parental BMI could not be responsible for the greater obesity in post-term boys. Thus, we hypothesize that in utero events during the 2-3 extra weeks of gestation associated with post-term birth resulted in metabolic reprogramming in boys, leading to the early development of adiposity. A possible alternative mechanism involves genetic and/or physiological factors earlier in gestation that eventually led to post-term delivery.

The observed phenotypic changes also might be a consequence of altered glucocorticoid secretion, given the high physiological stress associated with the post-term intrauterine environment, with a possible increase in cortisol secretion associated with delayed parturition. The placenta stops growing before term, and its permeability diminishes progressively after the 36th week of gestation, so that at term, its functional reserve is already slight or absent.[26] By 43 weeks gestation, there is a significant reduction in oxygen content in umbilical blood.[26,27] Adult males who experienced intrauterine growth restriction might have an altered response to stress, related to the differing long-term effects on autonomic and hypothalamic-pituitary-adrenal functions between the sexes.[28] Thus, males may be more susceptible to the stress associated with prolonged gestation. Alternatively, physiological stressors might affect adipogenesis or appetite regulation in post-term males. Furthermore, although postnatal socioeconomic factors might have contributed to adiposity in the post-term subjects, this is unlikely given the observed sex-dependent influence on adiposity.

We recognize some limitations in our study, particularly the exclusion of nearly two-thirds of the original cohort because of insufficient data. However, the distribution of excluded subjects in the term and post-term groups approximates that of the study cohort, and thus we believe that the study group is representative of the original cohort. Post-term births make up a limited proportion of all births, and it is not surprising that our post-term cohort was relatively small (n = 37) compared with the total number of recruited subjects (n = 525). Therefore, verification of our findings in larger population-based studies is important.

In conclusion, post-term birth is likely to increase the risk of obesity, insulin resistance, and metabolic syndrome in these males in adult life. Studies examining these possible metabolic changes, and whether the changes in adiposity persist or are amplified through adult life, are needed. ■

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