

Size at Birth Predicts Age at Menarche

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ABSTRACT. *Objective.* This study examines the relationship of intrauterine growth, measured by size and maturity at birth, to age at menarche, while also considering a wide range of other factors that may affect maturation. The research is motivated by the current debate about the importance of the prenatal environment as a determinant of later disease risk.

Methods. Data were collected during the Cebu Longitudinal Health and Nutrition Survey. This community-based study has followed a cohort of several thousand Filipino infants since their birth in 1983 to 1984. Participants live in urban and rural communities of Metro Cebu, the second largest metropolitan area of the Philippines. The analysis sample includes 997 girls 14 to 15 years of age. The main outcome measure is age at menarche, determined from girls' self-report of the month and year of first menses. Factors that influenced age at menarche were identified using Weibull parametric survival time models. The main exposure variables of interest included weight and length (measured by trained field staff) and gestational age (assessed from mother's reported date of last menstrual period, augmented by clinical assessments at birth). The analysis also takes into account a wide range of other factors that are likely to affect age at menarche. These include the girls' early postnatal growth rates, premenarcheal body composition (body mass index and skinfold thicknesses measured at 8 years), current diet (measured by two 24-hour dietary recalls), and socioeconomic conditions of the household in which they live. We also assessed the contribution of maternal characteristics, including age at menarche, height, and nutritional status while pregnant with the study child.

Results. The median age at menarche calculated from the hazard model is 13.1 years, with 50% of girls attaining menarche between 12.4 and 13.9 years. Earlier menarche is characteristic of girls who live in urban, higher socioeconomic status households, as indicated by higher maternal education, better housing quality, and possession of assets, such as a TV or refrigerator. Age at menarche is significantly associated with birth characteristics. Although birth weight alone was not significantly related to age at menarche, girls who were relatively long and thin at birth (>49 cm, <3 kg) attained menarche ~6 months earlier than did girls who were short and light (<49 cm, <3 kg). This effect of thinness at birth is most pronounced among girls with greater than average growth increments in 6 months of life. The effects of birth size are not modified when body mass index and

skinfold thicknesses at 8 years are taken into account. Effects of birth size on age at menarche also remain significant when maternal nutritional status during pregnancy and the girl's current diet and socioeconomic indicators are taken into account.

Conclusions. The study provides additional evidence of fetal programming of later health outcomes by showing that future growth and maturation trajectories are established in utero. Furthermore, rapid postnatal growth potentiates the effects of size at birth and is related independently to earlier pubertal maturation. *Pediatrics* 2001;107(4). URL: <http://www.pediatrics.org/cgi/content/full/107/4/e59>; birth weight, fetal programming, menarche.

ABBREVIATIONS. CLHNS, Cebu Longitudinal Health and Nutrition Study; BMI, body mass index.

An increasing body of evidence supports the hypothesis that intrauterine or early infancy exposures affect chronic disease risk later in life. The strongest evidence relates small size at birth to elevated blood pressure, coronary heart disease mortality, and altered glucose metabolism and type 2 diabetes (see recent reviews).¹⁻⁵

Relatively little attention has been paid to intermediate health outcomes that may be antecedents to chronic disease. This is important, particularly when the intermediate outcomes are affected by intrauterine factors and, in turn, affect the risk of chronic disease outcomes. The timing of pubertal maturation may be one such factor. Early maturation in girls is a well-established risk factor for breast cancer^{6,7} and overweight.^{8,9} Furthermore, early maturation is of public health interest because of its association with early initiation of sexual activity,¹⁰ which, in turn, has numerous health, demographic, and social consequences.

Although investigators have documented a trend toward earlier pubertal development in the United States¹¹ and Asia,¹² the exact causes of this trend have not been identified. The possible contribution of prenatal factors has not been adequately explored.

Epidemiologic evidence relating intrauterine growth to pubertal maturation is sparse. The timing of puberty was examined among Swedish adolescents who experienced adverse perinatal events, including maternal preeclampsia, preterm delivery, or intrauterine growth retardation manifested by small size for gestational age at birth.¹³ Girls who were small for gestational age had earlier menarche than did those of normal size for gestational age. However, controlling for postnatal growth patterns elim-

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inated the effect of birth size, and no effects of perinatal factors on pubertal timing were found among boys. In a large cohort of British women, Cooper et al¹⁴ found opposite effects of intrauterine and postnatal growth: girls who were heavier at birth had later menarche, but those who were heavier at 7 years had earlier menarche. Lumey and Stein¹⁵ found no differences in mean age at menarche among women exposed to famine conditions in utero compared with unexposed women, despite the lower birth weights associated with such exposures. No longitudinal studies have yet documented a relationship of size at birth to pubertal maturation in girls from developing countries.

Most literature on girls growing up under conditions of poverty in developing countries shows a pattern of delayed maturation associated with a history of undernutrition throughout childhood. For example, Khan et al¹⁶ found stunting by 3 years to be a significant predictor of later menarche among Guatemalan girls. Similarly, Simondon et al¹⁷ found delayed maturation among girls who were stunted during the preschool years. However, neither of these studies examined the effects of birth characteristics and subsequent child growth on age at menarche.

The present study examines the relationship of weight, length, and gestational age at birth to the timing of menarche in a cohort of girls followed from birth through adolescence. The analysis takes into account a wide range of other factors that are likely to affect age at menarche, including early postnatal growth rates, premenarcheal body composition, diet, and socioeconomic factors, as well as maternal age at menarche, height, and nutritional status during pregnancy.

METHODS

Sample

The analysis is based on data from the Cebu Longitudinal Health and Nutrition Survey (CLHNS).^{18,19} This survey follows a 1-year birth cohort from randomly selected urban and rural barangays (local administrative units) in Metro Cebu, Philippines. Cebu is the second largest and most rapidly growing metropolitan area of the Philippines. The CLHNS sample is economically and ecologically diverse. Approximately three-quarters of sample households are in urban neighborhoods ranging from poor, high-density squatter areas to relatively more affluent periurban areas. Some rural households are more isolated, located in the mountains or nearby small islands, whereas others are in small rural towns.

The initial CHLNS sample was drawn by contacting all pregnant women in the 33 selected barangays. Those who gave birth in a 1-year period (1983–1984) were included in the baseline study in which women were interviewed during pregnancy and at bi-monthly intervals until the child turned 2 years old. Follow-up surveys were conducted in 1991 to 1992, 1994 to 1995, and 1998 to 1999.

The 1998 to 1999 survey located and interviewed 997 nontwin girls (69% of female single live births in the CLHNS cohort). The analysis sample includes 966 girls 14 to 15 years old, who had complete information on birth characteristics and anthropometry at 8 years. Compared with 477 singleton girls born alive but lost to follow-up or excluded because of missing data, the analysis sample slightly overrepresents rural households but does not differ significantly in terms of total household income, assets, parental age and education, or birth order.

Data

All data were collected during face-to-face interviews in the respondents' homes. Children were measured immediately after birth, bimonthly until 2 years of age, and during follow-up surveys at ages 8 to 9, 11 to 12, and 14 to 15 years. Birth weight was initially measured by birth attendants. In addition, infant weight and length were measured by project staff as soon as births were reported. Length was measured using custom-made length boards. Gestational age was calculated from the date of the mother's last menstrual period. For low birth weight infants or in the case of pregnancy complications, gestational age was estimated from Ballard clinical assessments performed by trained nurses. Anthropometry at age 8 years included height, weight, and triceps and subscapular skinfold thicknesses. Mother's anthropometry included height, weight, and triceps skinfold thicknesses during the third trimester of pregnancy and within several days of giving birth. We use the triceps measurement during pregnancy and immediate postpartum body mass index (BMI) as indicators of maternal nutritional status. All anthropometric data were collected by highly trained field staff using standard equipment and measurement techniques. Interobserver reliability was checked on a regular basis.

During the 1994 to 1995 and 1998 to 1999 surveys, girls were asked to report their menarcheal status and the month and year of their first menstrual period. Concordance in reported dates from the 2 surveys was high. Mother's were asked to recall their age at menarche, reported in whole years. Numerous studies have proven the reliability of recall, particularly when the interval between the event and the recall is short, as is the case when young adolescents are asked to recall menarche.^{20,21}

The analyses use the girls' dietary and anthropometric data from the 1991 (age 8 years) survey, when none of the girls had yet attained menarche. In the 1991 survey, dietary intake was determined using a food frequency questionnaire. Items were selected as those most commonly reported in multiple 24-hour dietary recalls during earlier rounds of the survey. Energy and fat intakes were calculated using comprehensive food composition tables for the Philippines produced by the Food and Nutrition Research Institute.²² Low fat intake was defined as <10% of total energy from fat. Mother's diet during pregnancy was estimated from a 24-hour dietary recall. A diet factor score—based on intake of energy, protein, fat, iron, and calcium—was calculated to represent maternal diet quality.

Household socioeconomic status when the child was 8 years old was represented by a standardized factor score derived from household income, ownership of items such as a television and refrigerator, mother's educational attainment, urban or rural residence, and quality of housing materials.

Analysis Methods

The outcome of interest is age at menarche. For descriptive analysis, the girls were divided into 3 groups representing early (<12.1 years), average (12.1–14 years), or late (>14 years) maturation. Premenarchal girls were classified as late maturing because all were 14 years old or older. The early and late groups represent those girls whose age at menarche was approximately >1 standard deviation from the sample mean. Sociodemographic differences among the groups were tested using 1-way analysis of variance for continuous variables and χ^2 tests for categorical variables.

Parametric maximum likelihood survival models (the Weibull procedure in *Stata, Version 6*)²³ were used to examine the relationship of birth characteristics to age at menarche, controlling for a series of potential confounders and other determinants of age at menarche. Premenarcheal girls were treated as censored observations. Weibull estimates were similar to estimates from Cox proportional hazard models, but the Weibull procedure has the added advantage of allowing calculation of predicted survival time or, in this case, age at menarche.

RESULTS

Characteristics of the Sample

Approximately 95% of the girls had reached menarche at the time of the survey. The median age at

menarche calculated from the hazard model is 13.1 years, with 50% of girls attaining menarche between 12.4 and 13.9 years. Earlier menarche is characteristic of girls who live in urban, higher socioeconomic status households, as indicated by higher maternal education, better housing quality, and possession of assets, such as a TV or refrigerator (Table 1). A significantly higher proportion of early maturing girls were firstborn. Mother's age at menarche was younger among early maturing girls. There are significant differences in length between early and late maturing girls at birth. By 6 months old, all intergroup length differences were significant at the $P < .01$ level. This suggests that earlier maturing girls are already on a significantly different growth trajectory from birth.

Multivariate Models

A set of alternate model specifications is used to sequentially test the effects of birth characteristics, premenarcheal (8 years) body composition, and early postnatal growth as proposed by Lucas et al.²⁴ All of the models control for gestational age to allow for the interpretation of small birth size as a result of intrauterine growth restriction rather than prematurity. An additional set of models examined the effects of maternal nutritional status during pregnancy. Results from the multivariate survival analysis, in the form of hazard ratios and t statistics are presented in Tables 2 and 3.

Relationship of Birth Characteristics to Age at Menarche

There was no significant relationship of birth weight or small size for gestational age to age at menarche, except when birth length was taken into consideration. Given this result, subsequent analyses included variables that jointly characterized birth weight and length. For simplicity, 4 groups: long/light ($n = 181$), long/heavy ($n = 291$), short/light ($n = 375$), and short/heavy ($n = 119$) were defined using the median values for birth weight (3.0 kg) and length (49 cm). Mean age at menarche calculated

from the survival model was earliest (12.8 years) among long/light girls and latest (13.3 years) among short/light girls. Only 3 of the 51 premenarcheal girls were in the long/light group. In the first multivariate model (Table 1, column 1), with short/heavy girls as the reference group, being long and light at birth results in the highest hazard (1.61; 95% confidence interval: 1.27–2.04) and, therefore, the earliest age at menarche.

Effects of Premenarcheal Body Composition

As expected, higher BMI and larger sum of skinfolds at 8 years were strongly associated with earlier menarche (Table 1, column 2). Height at 8 years was not included in the models, because stature is more clearly an alternate indicator of pubertal maturation than is relative weight or fatness. The effects of birth characteristics remain essentially the same when BMI and skinfolds at 8 years are included in the model (column 3).

Effects of Other Factors Likely to Affect Age at Menarche

Although mother's and daughter's age at menarche were only weakly correlated ($r = 0.19$), later menarche in the mother was associated with a lower hazard, and, thus, later menarche in sample girls. Taller maternal stature was associated with later menarche. Higher socioeconomic status was significantly associated with earlier age at menarche. Higher total energy intake was not significantly related to age at menarche, but controlling for total energy intake, low fat intake was significantly associated with later menarche.

Inclusion of these maternal, dietary, and socioeconomic variables in the model did not alter the effects of birth characteristics (column 4). The relative importance of BMI versus skinfolds changed when dietary variables were added to the model, suggesting confounding of this relationship by diet. Dietary fat intake is more highly related to skinfold thicknesses ($r = 0.24$) than to BMI ($r = 0.02$).

TABLE 1. Sociodemographic Characteristics of Girls With Early, Average, or Late Menarche

	Early (≤ 12 Years Old) ($n = 143$)	Average (12.1–14 Years Old) ($n = 646$)	Late (> 14 Years Old) ($n = 208$)
Urban (%)*	82.4	75.7	60.4
Income (pesos/wk)†	478 \pm 435	400 \pm 411	325 \pm 396
Firstborn (%)*	29.6	20.2	15.5
Poorest quality housing (%)*	30.3	39.9	23.9
Household has TV (%)*	70.4	55.7	39.6
Household has refrigerator (%)*	33.8	22.5	9.7
Mother's education (highest grade)†	8.1 \pm 3.5	7.0 \pm 3.1	6.1 \pm 3.0
Mother's height (cm)	150.5 \pm 4.7	150.3 \pm 4.9	151.2 \pm 5.2
Mother's age at menarche†	13.5 \pm 1.5	14.0 \pm 1.5	14.5 \pm 1.6
Birth weight (kg)	3.01 \pm 0.41	2.99 \pm 0.41	2.95 \pm 0.43
Birth length (cm)‡	49.2 \pm 1.9	49.1 \pm 2.1	48.7 \pm 2.2
Length at 6 mo (cm)†	70.7 \pm 2.4	70.1 \pm 2.7	69.1 \pm 2.8
BMI at age 8 years (kg/m ²)†	15.2 \pm 1.7	14.7 \pm 1.2	14.3 \pm 1.0

* Significant intergroup differences, χ^2 , $P < .05$.

† Significant intergroup differences, analysis of variance, $P < .05$.

‡ Significant difference (analysis of variance, $P < .05$) when comparing average and late only.

TABLE 2. Results From Survival Analysis of Age at Menarche in Cebu Girls: Hazard Ratios and *t* Statistics Associated With Birth Characteristics, Early Postnatal Growth, and Child Premenarcheal Anthropometry

	1 Birth Effects	2 Age 8 Years Effects	3 Birth and Age 8 Years	4 + Other	5 Early Growth Interactions
Long/light	1.61 (3.91)*		1.57 (3.68)*	1.54 (3.51)*	
Long/heavy	1.37 (2.77)*		1.28 (2.18)†	1.29 (2.22)†	
Short/light	1.17 (1.42)		1.22 (1.81)‡	1.29 (2.26)†	
Gestational age	1.03 (1.71)‡	1.03 (1.92)‡	1.03 (1.94)‡	1.03 (2.09)†	1.03 (1.75)‡
Long/light/slow					1.33 (1.61)
Long/light/fast					1.78 (4.16)*
Long/heavy/slow					1.28 (1.68)‡
Long/heavy/fast					1.46 (2.87)*
Short/light/slow					1.24 (1.40)
Short/light/fast					1.40 (2.80)*
BMI		1.08 (2.44)†	1.09 (2.63)†	1.16 (4.38)*	1.16 (4.21)*
Skinfolds		1.08 (6.19)*	1.07 (5.72)*	1.02 (1.88)†	1.02 (1.54)
Mother's height				0.98 (-2.74)*	0.98 (-2.83)*
Mother's age at menarche				0.89 (-5.51)*	0.89 (-4.90)*
Total energy (1000 kcal)				1.06 (0.86)	1.13 (1.51)
Low fat (<10%)				0.86 (-1.95)‡	0.85 (-1.93)‡
Socioeconomic status				1.36 (6.09)*	1.31 (5.17)

* *P* < .01.

† *P* < .05.

‡ *P* < .10.

TABLE 3. Results From Survival Analysis of Age at Menarche in Cebu Girls: Hazard Ratios and *t* Statistics Associated With Maternal Characteristics During Pregnancy, Birth Characteristics of Infants, and Child Premenarcheal Anthropometry

	1 Maternal Characteristics Only	2 Infant Birth Characteristics Only	3 Maternal Plus Infant Birth Characteristics	4 Maternal Plus Infant Plus Child Anthropometry
Age at menarche	0.89 (-5.12)*		0.89 (-5.00)*	0.89 (5.08)*
Age at pregnancy	1.01 (0.87)		1.01 (0.88)	1.01 (0.98)
Height	0.98 (-3.15)*		0.98 (-3.15)*	0.98 (3.26)*
BMI after birth	1.05 (2.61)*		1.05 (2.78)*	1.02 (0.92)
Triceps skinfold thickness during pregnancy	1.01 (1.21)		1.01 (1.10)	1.02 (1.84)‡
Diet score	1.04 (1.13)		1.02 (0.78)	1.03 (0.97)
First pregnancy	1.22 (2.18)†		1.22 (2.17)†	1.17 (1.67)‡
Socioeconomic status	1.41 (8.11)*		1.38 (7.71)*	1.36 (6.78)*
Gestational age		1.03 (2.04)†	1.03 (2.07)†	1.03 (2.06)†
Birth weight		0.79 (-2.24)†	0.77 (-2.48)†	0.75 (-2.71)*
Birth length		1.08 (3.70)*	1.08 (3.54)*	1.06 (3.02)*
BMI (age 8 y)				1.14 (3.60)*
Sum of skinfolds (age 8 y)				1.03 (1.97)†

* *P* < .01.

† *P* < .05.

‡ *P* < .10.

Effects of Early Postnatal Growth

Faster growth rates in early infancy are significantly related to size at birth, and significantly predict earlier age at menarche. To explore the interactions of birth size and early postnatal growth, the birth weight and length groups were further characterized as slow or fast growing according to growth increments in the first 6 months of life. Fast growth was defined as a weight and/or length increment above the sample median, whereas slow growth was defined as weight and length increments below the median. The short/heavy girls are the reference group. Results from the hazard model are presented in Table 2 (column 5). The sample size for this analysis was reduced because some girls were missing length or weight measurements at 6 months old. To facilitate interpretation of the results, the predicted mean age at menarche for each group was calculated, holding all other variables constant at their means.

Figure 1 shows the groups arranged in ascending mean age at menarche (long/light, long/heavy, short/light, short/heavy). Within all but the short/heavy groups, faster growth is associated with earlier menarche, with the effect of faster growth being largest among the girls who were long and light at birth.

Effects of Maternal Nutritional Status

Birth weight and length are proxies for the intrauterine environment. An alternate way to characterize aspects of the intrauterine environment is to consider maternal nutritional status and other factors that might affect the course of pregnancy. We examined maternal anthropometric indicators, age, diet, parity, and age at menarche. Table 3 presents the results from alternate models, all of which control for socioeconomic status. Mother's postpartum BMI significantly predicts earlier menarche, but after con-

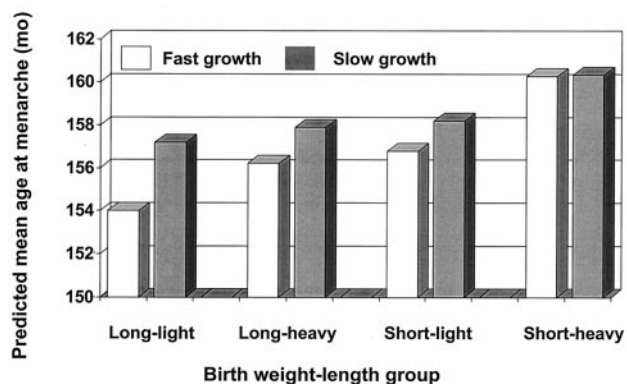


Fig 1. Predicted mean age at menarche in months according to weight/length groups and early postnatal growth rates of Cebu girls. Predictions are based on multivariate Weibull survival models, with all other characteristics held constant at their mean value.

trolling for socioeconomic status, maternal diet and skinfolds were not significant predictors. Despite the fact that maternal height, BMI, and primiparity significantly predict birth weight and length, these maternal characteristics and infant birth characteristics have independent and significant associations with age at menarche. The effects of infant birth characteristics are not modified by the inclusion of maternal nutrition variables and the effects of maternal characteristics are not modified by the inclusion of anthropometry of the girls at 8 years.

DISCUSSION

The main contribution of this research lies in its testing of the relationship of birth characteristics to the timing of menarche, while taking a wide range of postnatal factors into account. By having in-depth information on the mother; birth characteristics of the infant; subsequent growth patterns; and premenarcheal socioeconomic status, diet, and anthropometry, we can consider some of the important theoretical issues raised by critics of the fetal programming hypothesis. The results also contribute to our overall understanding of factors that influence the timing of menarche.

All of the analyses show a consistent and significant relationship of infant size at birth to age at menarche. Girls who were relatively long and light at birth attain menarche earlier. This effect is most pronounced among girls with more rapid early postnatal growth but is unmodified when BMI and skinfold thicknesses at 8 years are taken into account. The persistence of a birth size effect after controlling for numerous postnatal factors supports an independent role of the fetal environment. In the absence of more direct evidence of fetal metabolic or hormonal responses to intrauterine stress, it is not possible to conclude that fetal programming has indeed occurred. However, such an effect is biologically plausible because neuroendocrine development is susceptible to nutritional influences.²⁵ Animal and human studies have related prenatal growth retardation to adrenal cortical function,²⁶ resulting in exaggerated adrenarche manifested by elevated levels

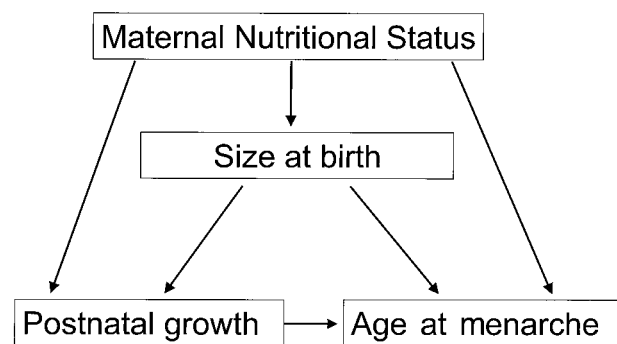


Fig 2. Conceptual model of hypothesized relationships among maternal nutritional status, size at birth, postnatal growth, and age at menarche.

of dehydroepiandrosterone sulfate and androstenedione.²⁷⁻³⁰

The prenatal environment may also influence the timing of menarche indirectly through postnatal growth (as shown in Fig 2). Postnatal growth is related to size at birth. Intrauterine growth-restricted infants, particularly those with weight deficits relative to their length, may have very rapid postnatal growth rates.^{31,32} Cebu girls who were relatively long and light at birth had the highest postnatal weight velocities of all the weight/length groups. Such effects are often dismissed as regression to the mean. However, adjustments in relative growth rates must be biologically driven, perhaps because of fetal programming. If intrauterine undernutrition results in greater metabolic efficiency,^{3,25} then rapid postnatal growth in previously growth restricted infants may reflect that greater efficiency. Infants may grow faster because they are metabolically programmed to take maximum advantage of the energy and nutrients likely to be provided by full breastfeeding in early infancy. Reprogramming of the insulin-like growth factor 1 axis would support such compensatory growth. This hypothesis is supported by evidence of higher insulin-like growth factor 1 levels in children with a history of low birth weight.³³

Overall, the results from the Cebu study suggest that rapid postnatal growth potentiates the effects of size at birth and independently accelerates pubertal maturation. This is consistent with other evidence that early maturation is associated with rapid postnatal growth related to metabolic disorders³⁴ or to recovery from severe illness or deprivation. The mechanisms relating accelerated postnatal growth to earlier maturation are not known.

The interpretation of the results as evidence of fetal programming rests, at least in part, on the assumption that relative thinness at birth represents evidence of intrauterine growth restriction and on the fact that the effects of birth size persist when postnatal growth is taken into account.²⁴ The strongest relationship with age at menarche occurs among girls who were long but relatively light at birth. This condition suggests less accumulation of body fat in the final trimester of pregnancy, most likely secondary to inadequate maternal nutrition (particularly because gestational age was taken into account).

Girls who were long but relatively heavy are less likely to have suffered intrauterine malnutrition, and despite comparable BMIs and skinfolds at 8 years, they do not mature as early as those girls who were long but underweight at birth. Similarly, when we look at the girls who were relatively short, those who were light attained menarche earlier than those who were relatively heavy at birth. The absence of an effect of growth velocity in the short/heavy girls is noteworthy but difficult to explain.

An additional strength of this study lies in its consideration of maternal factors likely to affect pregnancy outcome rather than relying on birth size alone as a proxy for intrauterine undernutrition or other forms of stress. The maternal nutritional environment was characterized by means of: 1) maternal skinfold thickness during pregnancy and immediate postpartum BMI as indicators of maternal energy reserves; 2) dietary intake during the third trimester of pregnancy; 3) height as a measure of nutritional history; and 4) age and primiparity as an indicator of ability to deliver adequate oxygen and nutrients to the fetus. The independent effect of maternal nutrition during pregnancy on age at menarche suggests that birth size alone fails to capture all of the relevant aspects of the maternal environment. At the same time, the remaining significant effect of birth size when maternal nutritional variables are taken into account suggests that some unmeasured aspects of the prenatal environment play an important role. The potential role of genetic factors could not be fully explored with this study design. However, inclusion of maternal height and age at menarche accounts for some potentially important genetic factors.

CONCLUSION

This study shows a pattern of earlier menarche among girls with evidence of intrauterine growth restriction, particularly when such restriction is followed by more rapid postnatal growth. The persistence of a significant relationship of size at birth to age at menarche even when a wide range of other factors is taken into account lends credence to the hypothesis that growth trajectories and timing of pubertal maturation are permanently affected by the intrauterine environment. More needs to be learned about the interactions of intrauterine and early postnatal growth and the independent effects of early childhood growth velocities as determinants of later developmental and health outcomes. Age at menarche is an outcome of interest not only as a marker of the pace of development but also as a potentially important intermediate determinant of later disease risk. Researchers have yet to identify the relative importance of prenatal factors versus later environmental and lifestyle factors as determinants of trends in earlier pubertal development. In the United States, where the prevalence of intrauterine and early infancy undernutrition is low, the contribution of such factors may be small. However, in developing countries where low birth weight and poor growth in early infancy are common, prenatal and early infancy environmental effects on pubertal maturation may be relatively large and worthy of attention.

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