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Influence of Perinatal Factors on the Onset of Puberty in Boys and Girls

Implications for Interpretation of Link with Risk of Long Term Diseases

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The authors examined the hypothesis that perinatal factors influence the onset of puberty. Children born as singletons in Uppsala, Sweden, in 1973–1977 were followed for height development before and during their school years (through 16 years of age). In all, 62 children born after preeclampsia, 129 born prematurely, 90 born small for gestational age, 175 born large for gestational age, 49 born short for gestational age, and 38 born tall for gestational age were compared with 688 "normal" children. Differences in age and height at puberty onset and age at menarche were analyzed using the *t* test and analyses of covariance. For boys, the mean age at puberty onset did not differ between normal boys and those with perinatal factors. Boys born small or short for gestational age were 4 cm shorter than normal boys, and those born large for gestational age were 3 cm taller than normal boys. Among girls, patterns for differences in height were similar. Girls born small for gestational age were 5 months younger than normal girls at the onset of puberty and menarche. Patterns of early childhood growth seemed to explain the relations between these perinatal factors and height and age at puberty. The authors conclude that body size at birth affects stature at puberty; in girls, smallness for gestational age is associated with earlier puberty. Associations between intrauterine exposures and disease risk may be confounded by, or mediated through, effects on adolescence. *Am J Epidemiol* 1999;150:747–55.

confounding factors (epidemiology); gestational age; growth; menarche; perinatal care; puberty; risk factors

The intrauterine environment of the fetus is thought to be important for long term health (1). A number of factors reflecting qualitative and quantitative aspects of intrauterine exposures to nutrients, oxygen, or placental hormones have been associated with chronic diseases (2). The so-called Barker hypothesis suggests that children born small for gestational age or with suboptimal growth during the first year of life are at increased risk of developing hypertension, glucose intolerance, and diabetes mellitus and to die of cardiovascular disease (2, 3). Epidemiologic findings provide evidence that placental dysfunction, as manifested through pregnancy toxemia, is associated with a reduction in breast cancer risk among daughters (4). Conversely, high birth weight, reflecting high exposure to placental hormones, has been associated with an excess risk of prostate cancer among sons (5). These observations support the hypothesis that target cells of the fetus are programmed for their future function by intrauterine exposures (6).

An important issue is whether perinatal factors also influence other, postnatal events that are important. Growth patterns during childhood and age at onset of puberty are suggested determinants of breast cancer risk in women and may affect the risk of cardiovascular diseases (3). Most importantly, early age at puberty onset and tall stature are risk factors for breast cancer (7, 8).

We explored whether the proposed effects of intrauterine exposures could be explained by an influence on puberty in a population-based longitudinal follow-up study of growth patterns in normal children and children with various perinatal factors. Our specific hypotheses were that 1) intrauterine exposures reflected by pregnancy aberrations (preeclampsia or prematurity) or by abnormal intrauterine growth (small or large for gestational age, short or tall for gestational age) influence age or height at onset of puberty or age at menarche and 2) the effects on puberty onset are associated with early childhood growth patterns.

MATERIALS AND METHODS

Source population and definition of cohorts

To select the study cohorts, we used two population-based Swedish registries, the Medical Birth Registry

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Abbreviation: SD, standard deviation.

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and the Inpatient Registry. The Medical Birth Registry was established in 1973 by the National Board of Health and Welfare to file information on all births taking place in Sweden. The information collected includes the personal identification numbers of the mother and child; the mother's reproductive history; and, with regard to the current pregnancy, estimated length of gestation, infant sex, birth weight and height, liveborn/stillborn status, single/multiple birth status, maternal diagnoses during pregnancy, obstetric procedures, infant diagnoses at delivery, and the parents' nationalities. A comparison of the registry data with medical record data for the period 1973–1981 revealed that the data were concordant for most of the recorded items, with some variability regarding diagnoses during pregnancy and infancy (9). The Inpatient Registry was started in 1965 by the National Board of Health and Welfare. Since then it has registered data on all hospital admissions, mostly in the six counties belonging to the Uppsala Health Care Region in the 1960s and 1970s and thereafter successfully expanding to include all counties in Sweden. The Inpatient Registry covers virtually all in-hospital care; it includes the patient's personal identification number and data on the hospital, diagnoses, timing of care, and surgical procedures. Registration has been found to be virtually complete and the quality of selected diagnoses high (10).

We selected from the Medical Birth Registry all children born alive as singletons at the University Hospital of Uppsala during the period 1973–1977 whose parents had been born in Sweden and were residing in the city of Uppsala at that time. Altogether, 9,808 children fulfilled these criteria.

All children in this source population were classified with regard to perinatal events from the combined data given in the Medical Birth Registry and the Inpatient Registry. A comparison group of children with no such events and cohorts of children "exposed to" gestational diabetes, preeclampsia, or premature delivery (<37 completed weeks of gestation) and children born small, large, short, or tall for gestational age were selected. Classification into these cohorts from the registry data is described in table 1. Among children in the registry-based source population, 1,360 had one or more of the

TABLE 1. Cohorts selected from the source population of singleton children born in Uppsala, Sweden, in 1973–1977, with parents who were living in Uppsala and had been born in Sweden (n = 9,808), using information from the Medical Birth Registry and the Inpatient Registry

Type of cohort (characterized by perinatal factors)	Source of information	Criteria for definition of perinatal factors
Gestational diabetes mellitus	Medical Birth Registry and Inpatient Registry	Any diagnosis of diabetes (ICD-7* code 250) in the mother before birth or as a postnatal diagnosis in the newborn
Preeclampsia	Medical Birth Registry and Inpatient Registry	Diagnosis of preeclampsia or eclampsia (ICD-7 code 637) before birth
Prematurity	Medical Birth Registry	Less than 37 completed weeks of pregnancy
Small for gestational age Large for gestational age	Medical Birth Registry	Diagnosis of small-for-gestational-age (ICD-7 code 777.10) or large-for-gestational-age (ICD-7 code 778.11) birth from the Medical Birth Registry, or calculated from the last menstrual period through Naegel's formula and the normal curve for weight per gestational age (standardized to 40 weeks), resulting in the following SDs*: small for gestational age, ≤–2 SD; large for gestational age, ≥2 SD
Short for gestational age Tall for gestational age	Medical Birth Registry	Diagnosis of short-for-gestational-age (ICD-7 code 777.30) or tall-for-gestational-age (ICD-7 code 778.15) birth from the Medical Birth Registry, or calculated from the last menstrual period and the normal curve for height per gestational age, with the following SDs: short for gestational age, ≤–2 SD; tall for gestational age, ≥2 SD
Normal children	*Medical Birth Registry and Inpatient Registry*	*No registered abnormality in pregnancy (ICD-7 codes 630–639 and 740–759) or at delivery (ICD-7 codes 651, 661, and 657.4); Apgar score at 5 minutes; no postnatal abnormality (ICD-7 codes 760–799)*

* ICD-7, *International Classification of Diseases*, Seventh Revision (22); SD, standard deviation.

above perinatal factors; the remaining 8,448 fulfilled the strict criteria for the reference cohort. Among these "normal" children, 1,360 were randomly selected to form the reference cohort. Thus, the primarily selected cohorts comprised 2,720 children altogether.

Cohorts under study

We aimed to follow these children longitudinally regarding growth (height and weight) during childhood and puberty. We used information obtained from routine visits to postnatal child health centers, which were made an average of 10 times during preschool years, and from regular medical check-ups provided during school years from ages 7 to 18. Routine measurements of height and weight are made by the school health service in the first, fourth, sixth, and eighth grades, corresponding to approximately 7, 10, 12, and 14 years of age, respectively. The measurements are carried out by trained child and school health nurses and are plotted on the Swedish Standard Growth Chart (11) (figure 1). These growth charts depict sex- and age-specific normal curves for height and weight for preschool and school-age children. The records of selected children in the study cohorts were retrieved up through 1995, by which time all of the children had reached the age of 18 years.

Medical records for the cohort children who had *remained* residents of Uppsala and had attended Uppsala schools after birth—i.e., those who were stable residents of this community—were searched, either in a central school archive or, for those who had recently graduated, in the archives of specific schools. The list of personal identification numbers from the Medical Birth Registry was linked to the population registry in order to obtain names and current addresses. Forty individuals were excluded because they either were deceased, had a protected identity, or had emigrated, leaving 2,680 children.

In all, records for 1,616 (60.3 percent) of the 2,680 children were located. The records of 64 students known to live in Uppsala could not be found. Among the remaining 1,000 students whose records could not be located, a 1997 residency check carried out in a 25 percent random sample revealed that 81 percent (209/257) lived outside the city of Uppsala. This fact and our extensive efforts to search for the archived records justified our assumption that we had included the vast majority of eligible children in our study base.

The cohorts under study comprised 810 children in the "exposed" cohorts (411 boys and 399 girls) and 806 children in the reference cohort (395 boys and 411 girls). The exposed cohorts were further restricted to include only those 637 children (79 percent) who had their weight or height at birth (per gestational age) classified from calculated values (table 2).

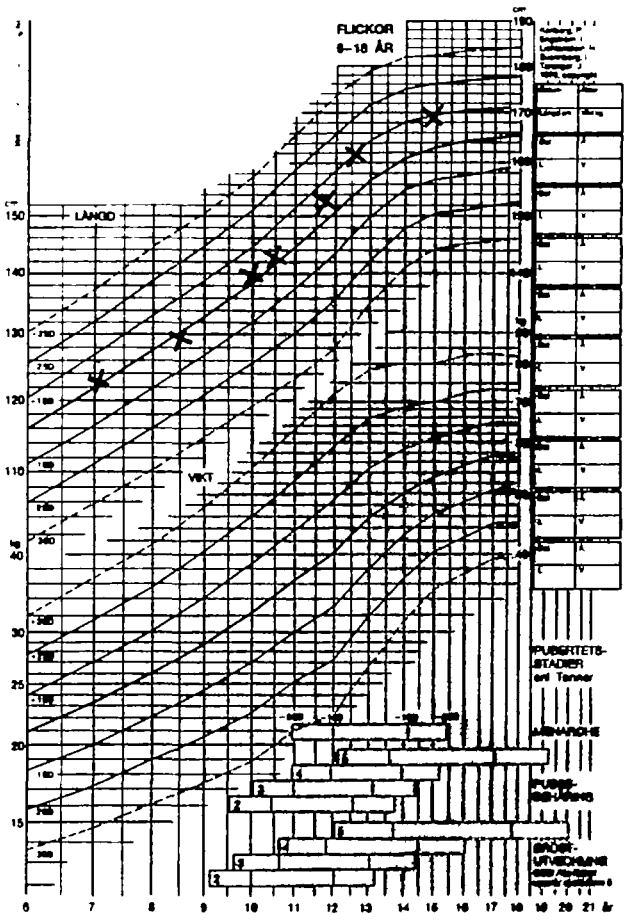

FIGURE 1. An example of the Swedish Standard Growth Chart (11) for girls aged 6–18 years, depicting height measurement values for one girl. SD, standard deviation.

Endpoint variables

Age and height at onset of puberty and age at menarche (for girls) were the endpoint variables. Classification of age at puberty onset and height at puberty onset entailed close scrutiny and interpretation of each individual's plotted curve for height values and determination of the time of a growth spurt pattern compatible with onset of accelerated pubertal growth. We applied a manual method, meaning that the examiner (one of four medical students) fitted three connected rulers (figure 2) to our height measurement values to estimate the point at which the stretch of the curve started to deviate by more than 12° from the prepubertal growth curve, representing a

TABLE 2. Numbers of children in the study cohorts who were identified and had available follow-up data from medical records, Uppsala, Sweden

	Boys		Girls		Both sexes	
	No. identified	No. with follow-up data	No. identified	No. with follow-up data	No. identified	No. with follow-up data
Normal children	395	368	411	320	806	688
"Exposed" cohorts						
All exposed children	369	319	268	231	637	550
Gestational diabetes*	5	5	2	2	7	7
Preeclampsia	45	36	33	26	78	62
Prematurity	82	71	66	58	148	129
Small for gestational age	54	48	47	42	101	90
Large for gestational age	121	106	80	69	201	175
Short for gestational age	31	26	27	23	58	49
Tall for gestational age	31	27	13	11	44	38

* These children were not analyzed further because of small numbers.

growth velocity of >6 cm/year (figure 3), which is a characteristic of pubertal growth (12). The deviation of at least 12° (figure 4) also corresponds to an increase in height velocity of approximately 2 cm/year and to an increase in height of at least 0.3 standard deviation scores per year, and is thus in accordance with the definition used by Karlberg et al. (13). Both age and height at this point were estimated and recorded on an abstraction form. The examiners were unaware of the cohort to which an individual belonged.

To assess interobserver agreement for the "three-ruler method," three of the medical students volunteered to classify age at puberty onset in an independent sample of height curves from the school records of 120 children (60 boys and 60 girls). The mean values for age at puberty onset were in fairly close agreement among the examiners: 11.4 (standard deviation (SD) 1.1), 11.1 (SD 1.0), and 11.1 (SD 1.0) years, respectively; and when values were mutually compared, differences were small: 0.3, 0.3, and 0 years.

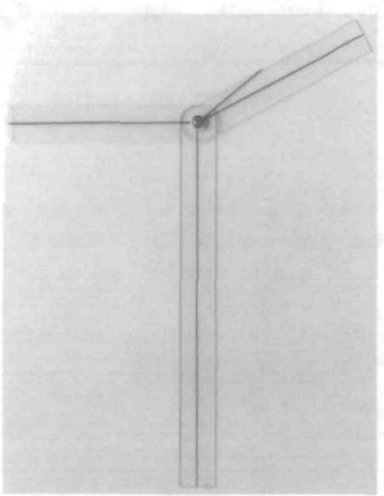

FIGURE 2. The device used to estimate age and height at onset of puberty among Uppsala, Sweden, children born in 1973–1977. The device consists of three connected rulers.

Growth patterns in childhood (ages 0–6 years)

To explore whether any effect of perinatal factors on adolescence could be explained by overall characteristics of early childhood growth, we included in our analyses estimators of parameters from a statistical growth curve model which describes a child's growth pattern during the period from birth to 6 full years of age. The model is a repeated-measurements model with random coefficients, where the mean of the model follows a first-order Reed model (14). For further details concerning the growth curve model, see the Appendix.

Analyses

Mean values for the endpoint variables age at puberty onset, height at puberty onset, and age at menarche were compared between the "exposed" cohorts and the reference cohort. In two-sided t tests, p values less than 0.05 were considered significant. The effects of perinatal exposures on the three endpoints were also investigated in an analysis of covariance. Covariates were maternal parity (primiparous vs. multiparous), maternal age (<25 years vs. ≥25 years), and all of the parameters in the growth curve model, defined in the Appendix. Covariates that did not significantly contribute to the covariance analysis were excluded. The purpose of this approach was to estimate whether inclusion of early (0–6 years) growth pattern estimators changed the conclusions from univariate t test comparisons between the groups.

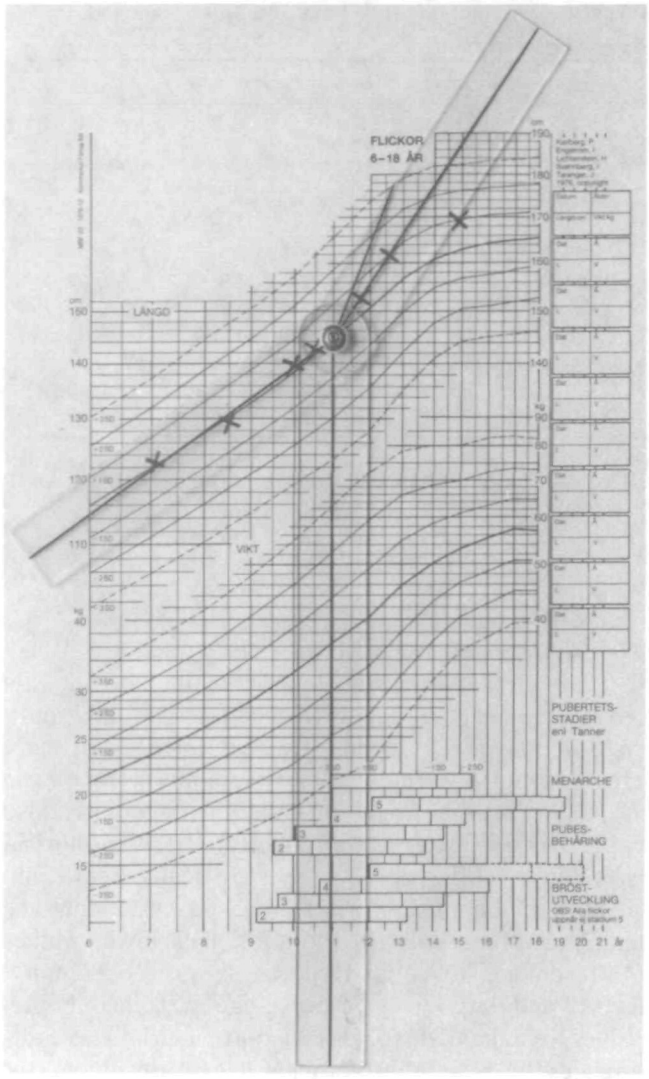

FIGURE 3. Demonstration of the procedure used to estimate the onset of puberty among Uppsala, Sweden, children born in 1973–1977. The left ruler is aligned with the assumed prepubertal growth measurement values, and the right ruler with the pubertal growth spurt values. The long vertical ruler indicates the child's estimated age at the onset of the pubertal growth spurt. SD, standard deviation.

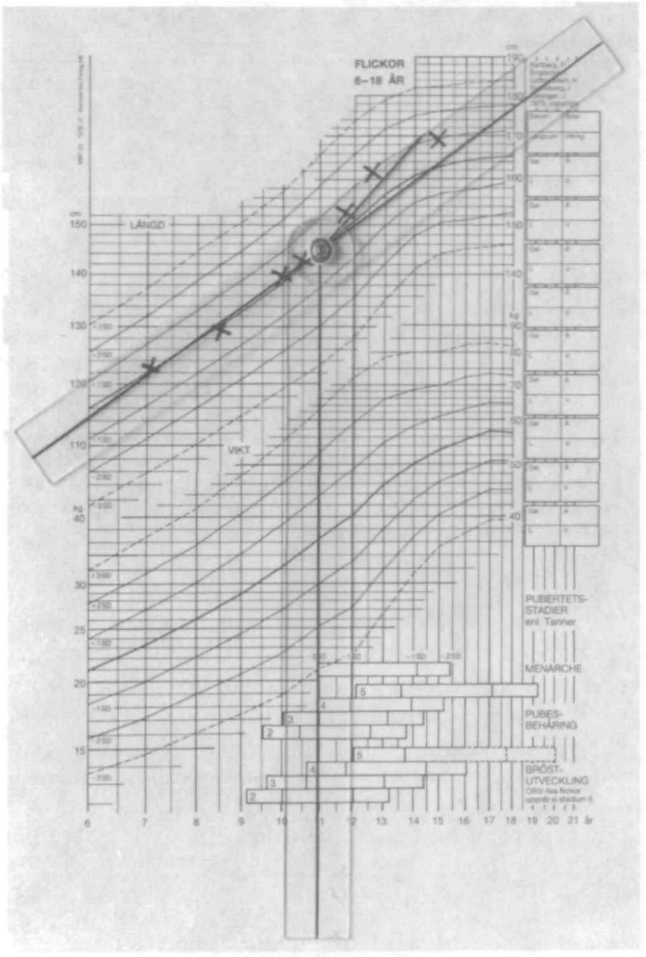

FIGURE 4. Confirmation that the definition of puberty onset has been satisfied, i.e., that the upward deviation (the angle marked on the right ruler) of the child's growth spurt is at least 12° (13). SD, standard deviation.

RESULTS

The numbers of children included in the analyses are shown in table 2. In the reference cohort, 688 (85 percent) of 806 children (93 percent of boys and 78 percent of girls) were classifiable with regard to the endpoint variables. Among all of the "exposed" cohorts, 550 (86 percent) of 637 children (87 percent of boys and 86 percent of girls) were entered into the analyses.

Boys

For "normal" boys, the mean age at onset of puberty was 12.1 years (table 3). None of the six groups differed statistically from the reference cohort according to perinatal factors. When the small-for-gestational-age group was restricted by excluding those with short-for-gestational-age status and the large-for-gestational-age group was restricted by excluding those with tall-for-gestational-age status, similar results emerged. Covariance analysis yielded similar results, i.e., no statistically significant difference.

Regarding height at onset of puberty, the small-for-gestational-age and short-for-gestational-age boys were significantly shorter (147.3 cm and 147.8 cm, respectively, vs. 151.9 cm; $p < 0.001$ and $p = 0.0096$) and the large-for-gestational-age and tall-for-gestational-age boys were significantly taller (155.2 cm and 155.1 cm, respectively, vs. 151.9 cm; $p < 0.001$ and $p = 0.0385$) than the normal boys. When growth patterns were included in the analysis of covariance, the significance of these differences vanished, indicating that differences in the overall early growth patterns could have

TABLE 3. Comparisons of age at onset of puberty and height at onset of puberty among normal boys and those "exposed" to perinatal factors, Uppsala, Sweden

Perinatal exposure group	Age at onset of puberty				Height at onset of puberty			
	No.	Mean age (years)	*p* for difference*	*p* for covariance†	No.	Mean height (cm)	*p* for difference	*p* for covariance
Normal children	368	12.1 (1.1)‡			368	151.9 (7.7)		
"Exposed" cohorts								
Prematurity	71	12.0 (1.1)	0.45	0.59	71	151.6 (7.3)	0.8	0.02
Preeclampsia	36	12.0 (0.9)	0.72	0.54	36	151.8 (6.6)	0.96	0.93
Small for gestational age	48	12.1 (1.2)	0.97	0.78	48	147.3 (7.4)	<0.001	0.65
Large for gestational age	106	12.0 (1.2)	0.38	0.60	106	155.2 (8.2)	<0.001	0.60
Short for gestational age	26	12.4 (1.0)	0.29	0.52	26	147.8 (6.3)	0.0096	0.30
Tall for gestational age	27	11.9 (1.3)	0.34	0.35	27	155.1 (7.8)	0.0385	0.65

* *t* test for the difference between the exposed cohort and the normal cohort.
† Analysis of covariance including maternal age (<25 years vs. ≥25 years), parity (1 child vs. ≥2 children), and parameters from the growth curve function (ages 0–6 years) (see Appendix). Covariables were only included if they contributed significantly.
‡ Numbers in parentheses, standard deviation.

explained the associations between these factors and endpoint variables. Prematurely born boys were equally as tall at puberty onset as boys in the reference cohort. When growth parameters were taken into account, a statistically significant difference emerged, indicating that there was a negative effect of prematurity.

Girls

Comparison of ages at puberty onset among girls revealed that prematurely born girls had a somewhat (nonsignificantly) higher age at puberty onset than "normal" girls (11.3 years vs. 11.1 years) (table 4). We found that small-for-gestational-age girls experienced onset of puberty an average of 0.4 years (about 5 months) earlier than normal girls (10.7 years vs. 11.1 years; $p = 0.022$), with a similar pattern being seen after exclusion of girls born short for gestational age. When the growth pattern estimators were included in the covariance analyses, the difference between the groups was no longer significant. Thus, differences in early growth patterns were likely to explain this effect on age at puberty onset. Short-for-gestational-age girls also experienced a lower age at puberty onset than normal girls, but the difference was not statistically significant. As for height at puberty onset, small-for-gestational-age and short-for-gestational-age girls had lower values (140.3 cm and 139.1 cm, respectively, vs. 146.2 cm; $p = 0.034$) and large-for-gestational-age girls had higher values (148.4 cm; $p < 0.03$) than normal girls. These differences became nonsignificant after adjustment for early growth patterns in the covariance analyses.

Normal girls had an estimated mean menarcheal age of 13.1 years, based on data from 263 girls for whom

TABLE 4. Comparisons of age at onset of puberty, height at onset of puberty, and age at menarche among normal girls and those "exposed" to perinatal factors, Uppsala, Sweden

Perinatal exposure group	Age at onset of puberty				Height at onset of puberty				Age at menarche			
	No.	Mean age (years)	*p* for difference*	*p* for covariance†	No.	Mean height (cm)	*p* for difference	*p* for covariance	No.	Mean age (years)	*p* for difference	*p* for covariance
Normal children	320	11.1 (1.0)‡			320	146.2 (7 3)			263	13.1 (1.0)		
"Exposed" cohorts												
Prematurity	58	11.3 (1.0)	0.08	0.17	51	145.4 (6.9)	0.49	0.23	58	13.2 (1.0)	0.54	0.18
Preeclampsia	21	11.1 (0.8)	0.87	0.80	21	144.9 (7.1)	0.43	0.57	26	12.9 (1.0)	0.38	0.28
Small for gestational age	35	10.7 (1.0)	0.022	0.11	35	140.3 (7.3)	<0.0001	0.22	42	12.7 (1.1)	0.032	0.33
Large for gestational age	61	11.1 (1.0)	0.82	0.92	61	148.4 (8.4)	0.034	0.89	69	13.0 (1.1)	0.42	0.39
Short for gestational age	18	10.6 (1.2)	0.06	0.14	18	139.1 (6.5)	<0.0001	0.40	23	12.8 (1.0)	0.148	0.71
Tall for gestational age	11	11.2 (1.3)	0.70	0.83	11	144.5 (10.0)	0.46	0.38	11	13.1 (1.5)	0.9	0.50

* *t* test for the difference between the exposed cohort and the normal cohort.
† Analysis of covariance including maternal age (<25 years vs. ≥25 years), parity (1 child vs. ≥2 children), and parameters from the growth curve function (ages 0–6 years) (see Appendix). Covariables were only included if they contributed significantly.
‡ Numbers in parentheses, standard deviation.

this information was available in the records. Small-for-gestational-age girls had a menarcheal age that was approximately 5 months lower than that of normal girls (12.7 years vs. 13.1 years; $p = 0.032$), and short-for-gestational-age girls showed a similar but nonsignificant difference. Inclusion of early growth patterns rendered the difference insignificant, indicating a possible role of early growth in mediating the effect on menarcheal age.

DISCUSSION

Our study, using population-based cohorts ascertained from registries and longitudinal growth measurements obtained from records, revealed some important associations between perinatal factors and age and height at onset of puberty. Children born light or short for gestational age were shorter at puberty onset and, conversely, those born heavy or tall for gestational age were taller at puberty onset than strictly defined "normal" children. These differences were associated with some characteristics of early childhood growth patterns. None of the studied perinatal factors seemed to influence age at onset of puberty in boys. However, we found that girls born small or short for gestational age experienced their growth spurt and menarche earlier, in association with some characteristic of growth in early childhood. This is in keeping with a general finding that females tend to react to perinatal traumatic factors (e.g., increased intracranial pressure) with precocious puberty more often than males do (15).

Advantages of our study design include the ability to define population-based cohorts that were followed longitudinally during their preschool and school years and throughout puberty and adolescence. We used a repeated-measurements growth curve model that fitted well to the data, and therefore we could quantitatively summarize growth patterns. However, some limitations in our data might have affected the results. The classification of perinatal events relied on registry data (the Medical Birth Registry and the Inpatient Registry) that were not validated. Misclassification of pre- and postnatal diagnoses, however, is likely to have been nondifferential with regard to our endpoint variables. Other factors were measurement-based, i.e., weight and height for gestational age, and such data are known to be reliable (9). Because the great majority of the records not retrieved concerned individuals who had left Uppsala, probably during childhood or their school years, our cohorts should have been representative of children in the stationary Uppsala population. It is reasonable that our findings of an association between perinatal events and adolescence could be generalized to a population as homogeneous as the Swedish one. Furthermore, the loss of observations may entail selection bias. (Among exposed children, there was a loss of 22 percent (173/810) of the subjects because of missing data on birth length and weight for gestational age and a loss of 11 percent (87/810) because of missing data on height during follow-up; among normal children, there was a loss of 15 percent (118/806) because of missing registry data.) It is not likely that losses in the registry information would be differential with regard to pubertal events. However, individuals with nonclassifiable endpoint data may be those with a delayed onset of puberty, precluding observations in the most extreme outcome groups. Our subjective classification of age at onset of puberty surely entails misclassification. The facts that such misclassification would be independent of cohort status (observers were blinded) and that the interobserver agreement for the method was good imply that our method was useful and informative. Our figure for age at pubertal onset in girls (11.1 years in normal girls) fits with the pubertal growth spurt model as described by Gasser et al. (16), who reported a figure of 11.2 years. Our mean menarcheal age of 13.1 years in normal girls is also well in line with Swedish data using the status quo method, which yielded an estimate of 13.2 years (17).

In boys, we found no association between perinatal factors and age at onset of puberty. We noted above that girls who were born small for gestational age or short for gestational age, on average, started their growth spurt earlier than normal girls. In another population-based sample of children in Sweden (18), the large majority of children born small for gestational age had a catch-up in height and a somewhat earlier growth spurt. A minority, lacking catch-up growth, had their peak height velocity in normal time. However, in that study, boys and girls were not analyzed separately (18). Since the statistical associations with both age at puberty onset and menarcheal age vanished when early growth patterns were considered as covariates, it is likely that *some characteristic* (as quantified by the growth curve model) of early growth mediated the effect. The hypothesis that the pattern of childhood growth may influence pubertal maturation was raised in a study of Indian girls adopted in Sweden (19, 20). It was found that short stature at arrival followed by fast catch-up growth was associated with early age at menarche. We intend, in separate analyses, to explore in detail the influence of specific early-childhood growth patterns on pubertal growth.

Neither age at puberty onset nor menarcheal age was influenced by prematurity or preeclamptic pregnancy, both of which could entail differences in the duration and level of intrauterine exposures. It may seem sur-

prising that being born small for gestational age had an effect on puberty but not maternal toxemia, since placental dysfunction is believed to be a common pathway of the two (2, 4). However, these conditions are heterogeneous and may reflect different degrees of involvement in placental pathways. Furthermore, it could be that preeclampsia, classified from registry data, represents less serious conditions as compared with those underlying intrauterine growth retardation.

Our findings may be important in understanding the suggested link between intrauterine exposures and long term diseases. Age and perhaps height at onset of puberty may be predictors of cardiovascular disease in men (3) and are established risk factors for breast cancer in women (7, 8). When interpreting the reported epidemiologic associations between perinatal factors and these two major diseases in men and women, the effects on pubertal age or height may have principally two different implications. Firstly, the effect on puberty may lie in the causal pathway between perinatal exposure and disease occurrence. If so, this will provide important clues as to the etiologic mechanisms involved. Secondly, if intrauterine exposure is associated with disease risk and timing of puberty, but through separate mechanisms, then pubertal effects may be viewed as confounding the relation. Under this assumption, our results imply that (for instance) in studies of cardiovascular disease in *men*, stature needs to be considered but not timing of puberty; when studying breast cancer risk in *women*, age at pubertal onset and stature may be regarded as confounders. The judgement regarding the way in which pubertal events are related to perinatal exposures is complex and may justify using alternate approaches in epidemiologic analyses. As for the reported protective effect of maternal toxemia on breast cancer risk in daughters, our results—that girls born small for gestational age would actually be at increased risk for breast cancer by means of an earlier onset of puberty—suggest that this effect is real and, if anything, is likely to be underestimated (negatively confounded).

Clearly, the mechanisms for the links between "intrauterine exposure" and development in the pubertal period need to be clarified. Our results provide one clue: that early childhood growth patterns are likely to be important. We suggest that new, interdisciplinary research should focus on postnatal growth (e.g., catch-up growth) and its relation with perinatal factors (e.g., pregnancy toxemia). Furthermore, the effects of intrauterine exposures (e.g., levels of hormones and growth factors) and environmental exposures (e.g., nutrition) should be explored, as well as possible common genetic determinants for perinatal and subsequent events.

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APPENDIX

A Repeated Measurements Growth Curve Model

Suppose that there are m individuals. For the kth individual, n_k measurements are taken. Let Y_{ki} be the measurement of body height at time t_{ki}, $i = 1, 2, \ldots, n_k$, and further suppose that Y_{ki} is proportional to the height of the previous observation Y_{ki-1}. Thus,

$$Y_{ki} = Y_{ki-1}\lambda_{ki},$$

where λ_{ki} is a random proportionality factor that reflects the growth process. We will assume that the growth process has independent increments, which implies that λ_{ki} and λ_{ki-1} will be regarded as independent random variables.

Moreover, measurement errors, say ε_{ki}, should be taken into account in the model. They will be regarded as independent of the growth process. Suppose $\varepsilon_{ki} \sim N(0, \tau^2)$, where ε_{ki}, $i = 1, 2, \ldots, n_k$, are independent. The following model is set up:

$$\log Y_{ki} = \log Y_{ki-1} + \log \lambda_{ki} + \varepsilon_{ki}.$$

It is supposed that the mean follows the Reed "first-order model" (14) with a translated time scale. Experience has shown that the model describes growth in early childhood fairly well, and our data also support this. Suppose that

$$\text{Var}(\log \lambda_{ki}) = \sigma^2(t_{ki} - t_{ki-1}).$$

All of these model assumptions, together with some calculations, imply that $\log Y_{ki}$ is normally distributed, with means, variances, and covariances given by the following:

$$\left.\begin{aligned} &E(\log Y_{ki}) = \alpha_k + \beta_{k1}(t_{ki} + 1) + \beta_{k2}\log(t_{ki} + 1) + \beta_{k3}(t_{ki} + 1)^{-1},\ i = 1, 2, \ldots, n_k. \\ &\text{Var}(\log Y_{ki}) = \sigma^2(t_{ki} - t_{k1}) + \tau^2,\ i = 1, 2, \ldots, n_k. \\ &\text{Cov}(\log Y_{ki}, \log Y_{kj}) = \sigma^2 \min(t_{ki} - t_{k1}, t_{kj} - t_{k1}),\ \text{for } i \neq j,\ i, j = 1, 2, \ldots, n_k. \end{aligned}\right\}$$

α_k, β_{k1}, β_{k2}, β_{k3}, σ^2, and τ^2 are unknown parameters. When modeling the whole population, we assume, instead of a constant α_k, a model for the population with a random α_k. Suppose α_k, $k = 1, 2, \ldots, m$, are independently identically distributed and normally distributed, i.e., $\alpha_k \sim N(\alpha, \gamma^2)$, where α and γ are unknown. Then, by some calculation, we obtain

$$\left.\begin{aligned} &E(\log Y_{ki}) = \alpha + \beta_1(t_{ki} + 1) + \beta_2\log(t_{ki} + 1) + \beta_3(t_{ki} + 1)^{-1},\ i = 1, 2, \ldots, n_k;\ k = 1, 2, \ldots, m. \\ &\text{Var}(\log Y_{ki}) = \sigma^2(t_{ki} - t_{k1}) + \tau^2 + \gamma^2,\ i = 1, 2, \ldots, n_k;\ k = 1, 2, \ldots, m. \\ &\text{Cov}(\log Y_{ki}, \log Y_{kj}) = \sigma^2 \min(t_{ki} - t_{k1}, t_{kj} - t_{k1}) + \gamma^2,\ \text{for } i \neq j,\ i, j = 1, 2, \ldots, n_k. \end{aligned}\right\}$$

The models used in this paper are similar to models used by Lundbye-Christensen (21). When estimating the parameters, we use restricted maximum likelihood theory. The parameter estimators will be used as covariates in an analysis of covariance.