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Prenatal factors, childhood growth trajectories and age at menarche

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Background In recent studies a larger birth size has been shown to delay the timing of menarche. The mechanisms underlying this association are not clear, however, as birthweight is a predictor of body size in childhood, and a large body size is known to be associated with an early onset of menarche.

Methods Data from a representative British cohort of 2547 girls born in 1946 who were followed prospectively throughout childhood were used. Information was available on prenatal characteristics, birthweight, height, weight and social circumstances during childhood, and on age at menarche. Random coefficients models were used to estimate the individual trajectories in height and body mass index (BMI) up to age 7 years. The parameters identified by these models were then included in Weibull survival models for the timing of menarche together with birthweight.

Results Birthweight was found to positively influence height and BMI values at age 2 years, but not to affect their rates of change from age 2 to 7 years. Initial analyses showed low birthweight to be associated with an early onset of menarche, but after controlling for growth in infancy this effect was reversed, with girls who were heavy at birth reaching menarche earlier than others with similar infant growth. Rapid growth in infancy was also related to early pubertal maturation. The effects of birthweight and infant growth disappeared, however, when further controlled for growth from age 2 to 7 years.

Conclusions The effects of birthweight and growth in infancy on the timing of menarche seem to be mediated through growth in early childhood. These findings are consistent with the possibility that timing of menarche may be set *in utero* or early in life, although it may be modified by changes in body size and composition in childhood.

Keywords Birthweight, childhood growth, life-course epidemiology, menarche, prenatal, puberty

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Recent evidence has suggested that the onset of menarche may be linked to prenatal exposures,[1–3] with some studies showing that larger birthweight is associated with later menarche.[1,2] The biological mechanisms underlying this potential association are counter-intuitive since birthweight is a positive predictor of body size in childhood[4,5] and a large body size is known to be associated with an earlier age of onset of menarche.[6]

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The aim of the present study is to examine in more detail the relative impact of birth size and early-life growth on timing of menarche. Clarification of these biological mechanisms might help our understanding of the reported link between the intrauterine environment, adult body size and the risk of developing certain diseases later in life.[7–9]

Materials and Methods

Data

The Medical Research Council National Survey of Health and Development (NSHD) consists of a socially stratified sample of all children born in the first week of March 1946 in Britain and followed up prospectively at regular intervals to this date.[10] The cohort comprised 5362 single births, of which 2547 (48%) were girls.

Height and weight were measured prospectively from birth (for weight) or age 2 years (for height) throughout childhood (at ages 2, 4, 6, 7, 11 and 15 years) but only measurements up to age 7 years, i.e. measurements obtained before the pubertal growth spurt, are used in these analyses. Body mass index (BMI: kg/m^2) was calculated when measurements on both height and weight were available. The information on age at menarche is based on the mothers' reports when the girls were aged 15 years or—if menarche had not been reached by that time or the girl was not seen at age 15—recalled by the participants at the follow-up visit when 48 years old (n = 344). Data on potential determinants of age at menarche such as maternal age, birth order and birthweight were collected at the time of birth of the study participant, measured maternal height and reported paternal height when the participant was 6 years old, and number of younger siblings and father's occupation during her childhood.

Methods

To assess whether girls who reached menarche early had different characteristics from those who developed later, they were categorized according to whether their age at menarche was less than the mean observed in the cohort minus one standard deviation (SD), more than the mean plus one SD, or in between. These groups were defined respectively as 'early', 'late', or 'average', with the 'late' group including girls for whom menarche was known not to have occurred by age 15.

To relate birthweight to the sequential height and BMI measurements, standardized ranks were computed for each girl in each period and the average rank profiles calculated for each menarche group. Because of the lack of birth length measurements, standardized ranks in birthweight were used as proxies for the standardized ranks of height and BMI at birth. For the same reason an indicator of growth in height in the first 2 years of life was calculated by taking the difference between a girl's rank in height at age 2 years and her rank in birthweight. A similar indicator of change in BMI was generated as the difference between the rank in BMI at age 2 and the rank in birthweight. These rank differences were standardized to have mean equal to 0 and standard deviation equal to 1. Indicators of early childhood growth from age 2 to 7 years and changes in body composition for each girl in the study were estimated using piecewise linear models with random coefficients.[11–13] Random coefficients models do not need complete data to be fitted, as long as the missing values can be assumed to occur at random. Further the random coefficients can be modelled in terms of explanatory variables such as prenatal factors (details in the Appendix). For simplicity, the terms 'infancy' and 'early childhood' will be used hereafter when referring to the periods from birth to age 2 years and from age 2 to age 7 years, respectively, as used by Karlberg.[14]

Weibull survival models were used to estimate the hazard (rate) of reaching menarche[15] as this allowed inclusion of the subset of girls for whom age at menarche was only known to be greater than 15 years as censored subjects. Results are reported in terms of hazard ratios (HR) for a unit increase in value and are to be interpreted as relative increases (for HR >1) or relative decreases (for HR <1) in the hazard of attaining menarche. Thus, the timing of menarche is estimated to be earlier than in a baseline group when the HR is greater than 1.

To examine whether the effect of birthweight on timing of menarche was mediated through growth in height or changes in BMI the random coefficients capturing the individual trajectories in infancy or early childhood were sequentially added to the Weibull model which included birthweight. Significance and interactions were tested using likelihood ratio tests[16] and CI computed using a bootstrap algorithm.[17] Analyses were carried out in Stata 7[18] and Mplus.[19]

Results

Data description

A total of 2547 girls were recruited in 1946, but 106 died before they reached age 15 years. Age at menarche was known for 1974 girls and for a further 84 it is known that their menarche had not yet occurred by age 15, giving a total of 2058 out of 2441 (84%) subjects for analysis. Comparison of the prenatal and growth features of these 2058 girls versus the remaining 383 who did not have any information on age at menarche showed no substantial differences (e.g. *P*-value for the difference in mean birthweight between the two groups was 0.15). Information on prenatal and growth variables was not always available for all girls (Table 1), but the pattern of incompleteness did not appear to be related to their age at menarche. For a total of 2015 girls there was at least one measurement of height and weight by age 7 years.

The average age at menarche among the 1974 girls for whom the information was available was 13.1 years (SD = 1.2). Hence girls were categorized as 'early' if their age at menarche was less than 11.75 years old, 'average' if between 11.75 and 14.25 years, and 'late' if greater than 14.25 years. Table 1 shows the distribution of birth, parental and childhood variables by timing of menarche. Early maturers were, on average, slightly lighter at birth than late ones. They were also more likely to have taller and younger mothers, to be first-born, to have fewer younger siblings, and to be less likely to have had a father in manual work during their childhood. They also grew, on average, faster in infancy and were taller and heavier at all ages from 2 to 7 years.

Growth in early childhood

The profile of the average standardized ranks in height of the early maturers crossed the profiles of the other two groups of girls somewhere between birth and age 2 years (Figure 1). This suggests that the lighter weight at birth of the early maturers tended to be followed by catch-up growth in early life. A similar pattern was observed for the profiles of the standardized ranks in BMI except that the crossing occurred at a slightly later age (Figure 1).

Figure 2 shows the growth trajectory in actual height and BMI from age 2 to 7 years by timing of menarche. The average trajectories in height increased almost linearly with age, with a slight reduction in slope from age 4 years onwards. In contrast, the average trajectories for BMI declined with age up to 6 years and then mostly flattened out from age 6 to 7 years. In general, both height and BMI profiles shifted upwards if the girl was an earlier maturer, although for BMI this was true only from age 4 years onwards.

To estimate the individual trajectories in height and BMI separate piecewise linear random coefficients models were fitted

Table 1 Characteristics of girls with early, average or late menarche

		Timing of menarche[a]		
	N	Early (<11.75 years)	Average (11.75–14.25 years)	Late (>14.25 years)
All	2058	271	1467	320
Birth size				
Birthweight (kg)	2051	3.3 ± 0.47	3.3 ± 0.48	3.4 ± 0.52
Parental characteristics				
Mother's height (cm)	1821	161.5 ± 6.7	161.3 ± 6.7	160.7 ± 6.2
Mother's age (years)	1852	28.7 ± 5.6	29.0 ± 5.7	29.4 ± 5.8
Birth order[b,c]	2057			
1st	848	52.4	40.4	35.3
2nd	666	28.0	33.3	31.9
3rd+	543	19.6	26.3	32.8
Father's height (cm)	1493	173.3 ± 7.6	173.5 ± 8.2	173.0 ± 7.5
Father's manual occupation[c]	1970	55.5	58.5	63.3
Childhood factors				
Younger siblings[c]	1859			
0	858	51.1	47.0	38.4
1	549	31.3	29.4	28.6
2+	452	17.6	23.6	33.0
Growth				
In infancy				
Ranks change from 0 to 2 years[d]	1645	0.25 ± 1.00	0.00 ± 1.01	–0.22 ± 0.92
In childhood				
Height (cm):				
at age 2 years	1676	85.7 ± 4.5	84.8 ± 4.8	83.7 ± 4.7
at age 4 years	1805	103.5 ± 5.5	102.8 ± 5.0	101.2 ± 5.0
at age 6 years	1684	115.0 ± 5.3	113.7 ± 5.4	111.7 ± 5.0
at age 7 years	1840	121.1 ± 6.1	119.6 ± 5.6	117.7 ± 5.3
Body composition				
In infancy				
Ranks change from 0 to 2 years[e]	1576	0.10 ± 0.95	–0.01 ± 0.98	–0.05 ± 1.11
In childhood				
Body mass index (kg/m^2):				
at age 2 years	1582	17.5 ± 2.1	17.7 ± 2.5	17.6 ± 2.3
at age 4 years	1770	16.2 ± 1.6	16.1 ± 1.7	15.7 ± 1.6
at age 6 years	1681	16.0 ± 1.6	15.7 ± 1.4	15.4 ± 1.3
at age 7 years	1772	16.2 ± 1.8	15.7 ± 1.6	15.2 ± 1.3

[a] Unless stated otherwise, the values in each of the cells are: mean ± SD.

[b] Birth order was included among the maternal characteristics as a marker of *in utero* environment.

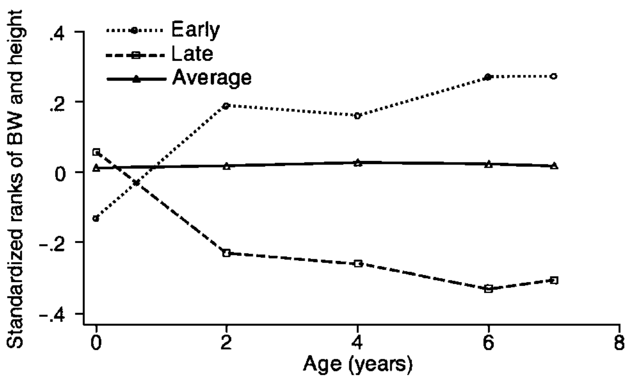
[c] The values in the 'Timing of menarche' columns are percentages.

[d] Growth in infancy was defined as the standardized difference between the rank in height at age 2 years and the rank in birthweight.

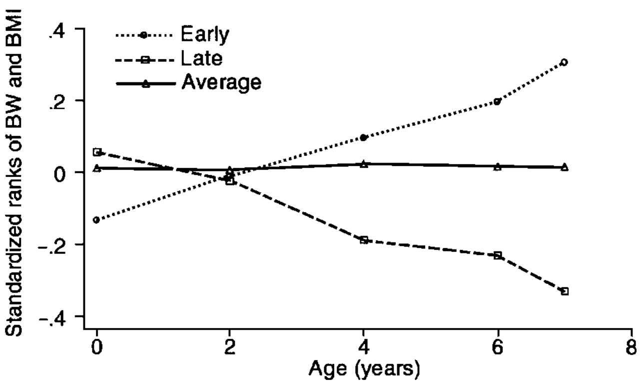
[e] Change in body composition in infancy was defined as the standardized difference between the rank in BMI at age 2 years and the rank in birthweight.

to the data. The piecewise model for height had a change of rate at age 4 years, to reflect the slowing of its rate, leading to three random coefficients being estimated for each girl: her height at age 2 years (intercept) and her rates of growth between ages 2 and 4 years, and between ages 4 and 7 years. The average intercept, estimated without accounting for explanatory variables, was 84.8 cm (standard error [SE] = 0.11 cm). The individual intercepts however varied around this average with a variance of 12.24, implying a 95% range of values between 75 and 94 cm. The estimated average rate of increase from age 2 to 4 years was 8.9 cm per year (SE = 0.06; 95% range: 6.2, 11.6 cm/year) while that from age 4 to 7 years was 5.7 cm per year (SE = 0.03; 95% range: 4.6, 6.7 cm/year).

To quantify the effects that prenatal factors might have on these coefficients, maternal characteristics, father's social class and number of younger siblings were included in the model as explanatory variables for the random coefficients (paternal height was excluded because of the large number of missing values). Results obtained including variables with a significance value of $P < 0.10$ are shown in Table 2. Birthweight and, to a



Time (years)	0	2	4	6	7
Early	216	216	238	223	234
Average	1172	1176	1289	1199	1321
Late	257	260	278	262	285
All	2058	1652	1805	1684	1840



Time (years)	0	2	4	6	7
Early	216	209	234	215	224
Average	1172	1128	1259	1198	1275
Late	257	245	277	268	273
All	2058	1582	1770	1681	1772

Figure 1 Profiles of average standardized ranks of birthweight (BW) and height and of birthweight (BW) and BMI by categories of timing of menarche (the numbers refer to the subjects contributing to each average value)

much lesser extent, maternal age had a positive effect on height at age 2 (an additional 1.70 cm for every kg and an additional 0.47 cm for every 5 years of mother's age) but no effect on the rate of growth at later ages. Maternal height influenced all three random coefficients: for every additional centimetre in maternal height there was an estimated increase of 0.64 cm in height at age 2 years, of 0.28 cm/year in the growth rate between age 2 and 4, and of 0.18 cm/year in the rate between 4 and 7 years. Birth order had a strong negative effect on height at age 2 (0.63 cm loss per older sibling) and a small negative effect on the two growth rates. The influence of socioeconomic circumstances are evident in the negative effects of paternal manual

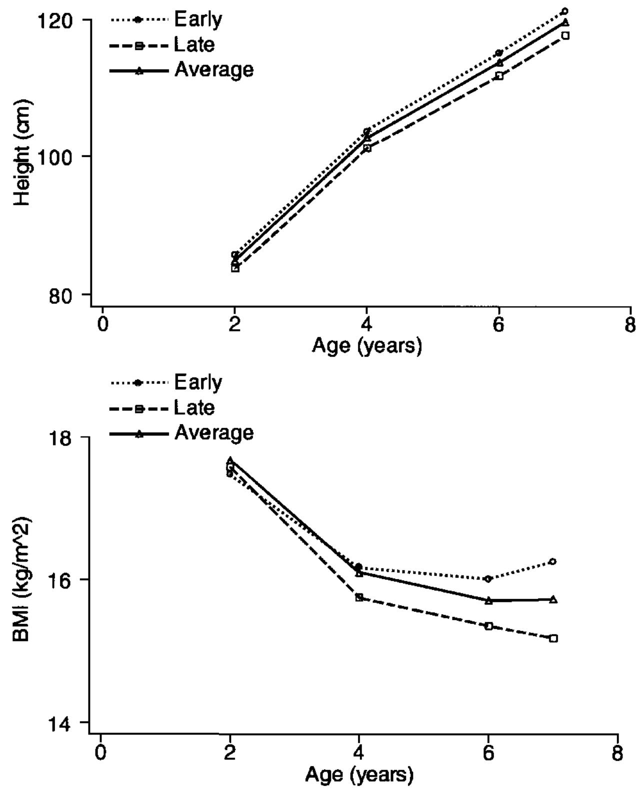


Figure 2 Profiles of average height and of body mass index (BMI) by categories of timing of menarche (the same numbers of subjects as in Figure 1 were used)

occupation on both height at age 2 and the rate of growth between 2 and 4 years, and in the fairly strong negative effects of number of younger siblings on the two growth rates.

The equivalent analyses of the BMI data were based on a piecewise linear random coefficients model with a change of rate at age 6 years and no change from age 6 to 7. The average BMI profile estimated without explanatory variables had an intercept at age 2 years of 17.0 kg/m^2 (SE = 0.05; 95% range: 11.8, 22.2 kg/m^2) and a rate of change from age 2 to 6 years of –0.33 kg/m^2 per year (SE = 0.02; 95% range: –0.56, –0.10 kg/m^2 per year). Of all the explanatory variables considered, only birthweight was found to influence the intercept at age 2 years, while paternal manual occupation reduced, although not significantly, the decline in BMI from age 2 to 6 by 0.03 kg/m^2 per year.

Birthweight, early childhood growth and timing of menarche

The separate effects on the timing of menarche of birthweight, growth, and changes in body size throughout infancy and childhood were estimated from univariate Weibull models (Table 3). The infancy variables are the standardized differences in ranks from birth to age 2 years (as estimated by random coefficients models) and the childhood variables are the rates estimated from the height and BMI random coefficients models. High birthweight was associated with a late menarche as the rate of onset of menarche was reduced by 4% (and, hence, menarche

Table 2 Growth in height and changes in body mass index (BMI) at ages 2–7 years: random coefficients models[a] (N = 2008)

	Height at age 2 (cm)		**Growth rate age 2–4 years (cm/year)**		**Growth rate age 4–7 years (cm/year)**	
Model for height	Coefficient	(95% CI)	Coefficient	(95% CI)	Coefficient	(95% CI)
Baseline	85.83	(85.45–86.21)	9.25	(9.05–9.45)	5.76	(5.66–5.86)
Birth characteristics						
Birthweight (kg)	1.70	(1.32–2.08)	–	–	–	
Parental characteristics						
Mother's height (cm)	0.64	(0.40–0.88)	0.28	(0.16–0.40)	0.18	(0.12–0.24)
Mother's age (5 years)	0.47	(0.29–0.65)	–	–	–	–
Birth order[b]	–0.63	(–0.81 to –0.45)	–0.07	(–0.15–0.01)	–0.03	(–0.07–0.01)
Father's manual occupation	–0.68	(–1.16 to –0.20)	–0.30	(–0.54 to –0.06)	–	–
Childhood factors						
No. of younger siblings[c]	–	–	–0.12	(–0.20 to –0.04)	–0.06	(–0.10 to –0.02)
	BMI at age 2 (kg/m^2)				**Rate age 2–6 years (kg/m^2/year)**	
Model for BMI	Coefficient	(95% CI)			Coefficient	(95% CI)
Baseline	16.96	(16.86–17.06)			–0.35	(–0.38 to –0.31)
Birth characteristics						
Birthweight (kg)	0.50	(0.38–0.62)			–	–
Parental characteristics						
Father's manual occupation	–	–			0.03	(–0.002–0.06)

[a] The random coefficients models were piecewise linear with a change in rate at age 4 years for height and at 6 years for BMI. For this latter model the slope between age 6 to age 7 years was estimated to be zero for all girls in the study, i.e. there was no random coefficient for this slope.
[b] Birth order is included among the maternal characteristics as a marker of *in utero* environment.
[c] This variable was not included among the explanatory factors for the intercept because of its timing.

Table 3 Univariate effects of birthweight, growth and changes in body composition on timing of menarche: Weibull model (N = 2008)

	HR[a]	**(95% CI)[a]**	**Test for interaction with birthweight**
Birthweight (kg)	0.96	(0.87–1.05)	–
Growth			
In infancy:			
Ranks change from 0 to 2 years[b]			$P = 0.79$
1st third	1	–	
2nd third	1.17	(0.93–1.35)	
3rd third	1.44	(1.21–1.66)	
Test for linear trend	$P < 0.001$		
In childhood:			
Height rate[c] (cm/year)			
2–4 years old	1.26	(1.19–1.37)	$P = 0.42$
4–7 years old	1.76	(1.48–2.15)	$P = 0.97$
Changes in body composition			
In infancy:			
Ranks change from 0 to 2 years [d]			$P = 0.32$
1st third	1	–	
2nd third	1.17	(0.97–1.41)	
3rd third	1.24	(1.08–0.48)	
Test for linear trend	$P < 0.001$		
In childhood:			
BMI rate[c] (kg/m^2/year)			
2–6 years old	2.10	(1.43, 2.91)	$P = 0.49$

[a] Hazard ratio; 95% bootstrapped CI (bootstrapped to account for the estimation step required to obtain the random coefficients).
[b] Growth in infancy is defined as the difference in ranks between the height at age 2 estimated by the random coefficients model and birthweight. This was then grouped into thirds.
[c] Height and BMI rates were estimated by the random coefficients model.
[d] Changes in body composition in infancy is defined as the difference in ranks between BMI at age 2 estimated by the random coefficients model and birthweight. This was then grouped into thirds.

was delayed) for every additional kilogram increase in birthweight, although this effect was not statistically significant. In contrast, the rate of onset of menarche increased with increasing thirds of the infant growth indicator (*P* for linear trend <0.001), with the hazard in girls who were in the top third being increased by 44% (Table 3). This trend continued in childhood with the strongest predictor of an early menarche being the yearly rate in height between age 4 and 7 years, when the hazard of reaching menarche increased by 76% for every additional cm/year increase in rate. The rate of onset of menarche increased with higher changes in ranks of BMI in infancy (Table 3). It also increased with greater BMI rates from age 2 to age 6 years. Since for most girls BMI decreased over these ages, this implies that girls with slower decline in BMI in childhood experienced earlier menarche. There was no indication that the effect of birthweight on timing of menarche was different for different levels of infant or childhood growth or changes in BMI (none of the tests for interaction were significant; Table 3).

The effect of birthweight on timing of menarche was re-examined by sequentially adding the infant and early childhood growth and BMI variables to the Weibull survival model for birthweight (Table 4). Controlling for the effect of growth in infancy pushed up the HR for birthweight from 0.96 to 1.17 (95% CI : 1.06–1.36) indicating that, for a given change in ranks from birth to age 2 years, heavier babies would have an earlier menarche. Controlling further for growth in height between ages 2 and 4 years reduced the HR for birthweight, which became closer to 1. Further inclusion of the coefficients for growth in height up to age 7 did not affect this result. By additionally including the indicators of change in BMI, the HR for birthweight increased slightly, but remained not significantly different from 1. By contrast, fast growth and heavier body composition in infancy and early childhood accelerated the onset of menarche even after adjusting for birthweight. Thus, faster growth in height and slower (or no) decrease in fatness between birth and age 7 years were found to significantly lead to earlier age at menarche. Further adjustment for parental characteristics did not affect these findings.

Discussion

In this paper, initial analyses showed that high birthweight was associated with a later onset of menarche. After taking into

Table 4 Models for the effect of birthweight on timing of menarche: Weibull model (N = 2008)

	Also including:									
	Growth in infancy		Growth in infancy and childhood up to age 4		Growth in infancy and childhood up to age 7		Growth in infancy and childhood and changes in BMI[a] in infancy		Growth in infancy and childhood and BMI profile	
	HR[b]	(95% CI)[b]	HR[b]	(95% CI)[b]	HR[b]	(95% CI)[b]	HR[b]	(95% CI)[b]	HR[b]	(95% CI)[b]
Birthweight (kg)	1.17	(1.06–1.36)	1.03	(0.92–1.16)	0.99	(0.88–1.12)	1.15	(0.97–1.40)	1.09	(0.87–1.30)
Growth										
In infancy:										
Ranks change from 0 to 2 years										
1st third	1	–	1		1		1		1	
2nd third	1.23	(1.02–1.42)	1.09	(0.91–1.32)	1.05	(0.89–1.31)	1.08	(0.87–1.27)	1.01	(0.86–1.24)
3rd third	1.60	(1.28–1.87)	1.25	(1.03–1.52)	1.17	(0.97–1.41)	1.22	(0.85–1.57)	1.04	(0.74–1.36)
Test for linear trend	$P < 0.001$		$P = 0.03$		$P = 0.17$		$P = 0.12$		$P = 0.74$	
In childhood:										
Height rate[b] (cm/year)										
2–4 years	–	–	1.20	(1.12–1.28)	1.17	(1.09–1.27)	1.17	(1.09–1.28)	1.19	(1.12–1.29)
4–7 years	–	–	–	–	1.29	(1.06–1.59)	1.23	(0.93–1.53)	1.34	(1.07–1.65)
Changes in body composition										
In infancy:										
Ranks change from 0 to 2 years										
1st third	–	–	–	–	–	–	1		1	
2nd third	–	–	–	–	–	–	1.21	(0.97–1.44)	1.21	(1.03–1.52)
3rd third	–	–	–	–	–	–	1.34	(1.07–1.57)	1.41	(1.16–1.74)
Test for linear trend	–		–		–		$P = 0.01$		$P < 0.001$	
In childhood:										
BMI rate[b] (cm/year)										
2–6 years	–	–	–	–	–	–	–	–	2.19	(1.34–3.15)

[a] Hazard ratio; 95% bootstrapped CI (bootstrapped to account for the estimation necessary to obtain the random coefficients).

[b] Growth in infancy was defined as the difference in ranks between the height at age 2 estimated by the random coefficients model and birthweight. Change in body composition in infancy was defined as the difference in ranks between BMI at age 2 estimated by the random coefficients model and birthweight. They were both grouped into thirds.

[c] All rates are estimated by the random coefficients model.

account growth in infancy, however, the effect of birthweight was reverted, with girls who were heavier at birth for a given rate of growth having an earlier onset of menarche. In addition, rapid growth in infancy was also associated with early pubertal maturation and this effect was not confounded by birthweight. Further inclusion of growth indicators from age 2 to 7 years reduced both the magnitude and the significance of the effects of birthweight and growth in infancy on timing of menarche indicating that they might be mediated through growth in early childhood.

The findings of the present study are consistent with those reported by others.[2,3] Persson *et al.*[2] showed that girls born small (or short) for gestational age were younger than normal girls at the onset of menarche but that this difference disappeared once patterns of early childhood growth were taken into account. In another study,[3] the effect of birthweight on age at menarche was found to be modified by birth length and growth in infancy: girls who were relatively long and light at birth attained menarche earlier than those who were short and light, with this effect being particularly marked among girls who grew fast in the first 6 months of life. A previous analysis of the data used in the present study[1] found a statistically significant positive effect of birthweight on age at menarche which became apparent after controlling for weight at age 7 years, but no account was taken of patterns of growth in infancy and early childhood.

Similarly to other studies,[4,5] parental height, maternal age, social class of the father, family size (as measured by birth order representing an intrauterine effect and number of younger siblings representing a postnatal social effect) and birthweight were predictors of height in early childhood. Our data seem to suggest that these factors may well operate through different mechanisms. Older maternal age and high birthweight shifted the growth trajectories upwards but had no effect on the rates of growth from age 2 to 7 years. Thus, whatever their maternal age or birthweight, children appeared to track along parallel growth trajectories from age 2 to 7 years. These observations may be interpreted as an indication that these factors exert their effect on height *in utero* or early in life, perhaps mediated through programming of lifetime patterns of secretion of, or sensitivity to, hormones that regulate growth.[20] In contrast, maternal height, which reflects partly genetic factors and partly social circumstances, and father's occupation influenced height at age 2 as well as the magnitude of the growth rates from age 2 to 7 years.

Advantages of our study include the representativeness of the sample and the availability of recorded data on perinatal characteristics as well as height and weight measurements throughout childhood. Measurement errors in height and weight and incompleteness of these data were taken into account by fitting random coefficients models. This allowed the analysis of a larger dataset because growth coefficients could be estimated for all girls with at least one measurement of height and BMI. There were some limitations, however. The value of the birthweight data was restricted by the lack of information on gestational age; moreover, the birthweight data might have been affected by measurement error and, hence, the observed effect on age at menarche might be biased. There is, however, no reason to believe that the degree of measurement error might have differed by age at menarche. The unavailability of height and weight measurement between birth and age 2 years did not allow us to compute more precise indicators of growth in infancy. We used instead proxy indicators based on the differences in ranks between birthweight and height (or BMI) at age 2 years. Despite their crudeness these measures seem to have captured, to a certain extent, some aspects of early postnatal growth. Although our findings seem to indicate that both fetal and early postnatal growth may be important determinants of the timing of menarche, unravelling the exact pathways through which these factors might operate would require more detailed data on pre- and postnatal growth than those available in the present study. Data on menarcheal age were based on mother's recall when the women were aged 15 years or, for a minority (17%), on the woman's recall when she was 48 years. It is unlikely, however, that the results were affected by substantial recall bias as the accuracy of recalled age at menarche to within one year has been shown to be high 40 or more years after the event.[21] Moreover, the mean menarcheal age of 13.1 years found in this study is similar to that reported by other contemporary British surveys.[6]

Body mass index values were used instead of weight. Their use was justified by the interpretability of the results. The joint analysis of height and BMI may capture both body size and body composition better than the joint analysis of height and weight. As Michels *et al.*[22] pointed out, when both height and weight are included in the model, within any given stratum of weight taller people will necessarily be leaner and thus height will reflect not only body size but also composition. In a model with height and BMI, however, height remains a measure of overall body size.

The effects of birth size and growth in infancy suggest that timing of menarche may be set *in utero* or infancy and that their effect may be mediated through early childhood growth. If so, this would have implications for the interpretation of the reported links between intrauterine environment and risk of certain adult diseases. For instance, high birthweight,[8,9] high stature[23] and early age at menarche[23] are known risk factors for breast cancer. However, it is not known whether birthweight exerts its influence on breast cancer occurrence through its association with childhood growth and timing of menarche or through other mechanisms. Clarification of these relationships will provide clues as to the aetiological mechanisms involved.

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Appendix

The piecewise linear random coefficients (multilevel) models used to analyse the repeated measures of height and BMI at ages 2, 4, 6 and 7, with one knot, respectively, at age 4 and at age 6 years, are defined below. They were used instead of, for example, quadratic functions because of the more direct interpretability of the parameters.

For ht_{it} representing the observed height for girl i at age t, $(I_{t \leqslant 4})$ being an indicator of whether t is less than or equal to 4 years, $(I_{t > 4})$ of whether t is greater than 4 years, and e_{it} representing independent normal errors with mean zero and variance σ^2_e,

$$ht_{it} = b_{0i} + b_{1i}\, t\, (I_{t \leqslant 4}) + 2b_{1i}\, (I_{t > 4}) + b_{2i}\, (t-2)\, (I_{t > 4}) + e_{it} \quad (1)$$

This model implies that the growth curve for a girl i is identified by her own coefficients b_{0i}, b_{1i} and b_{2i}. These subject-specific parameters are assumed to be normally distributed around their means (b_0, b_1, b_2), as

$$\begin{aligned} b_{0i} &= b_0 + u_{0i} \\ b_{1i} &= b_1 + u_{1i} \\ b_{2i} &= b_2 + u_{2i} \end{aligned} \quad (2)$$

where u_{0i}, u_{1i} and u_{2i} are normal variables with mean zero, and variance-covariance matrix Σ. For a subject i, (b_{0i}, b_{1i}, b_{2i}) represent respectively the value of the growth curve at age 2 (intercept), the growth rate between age 2 and 4 and the growth rate between age 4 and 7. These parameters can be allowed to be influenced by explanatory variables. For example, a model where birthweight (BW) is assumed to affect the intercept, and father's occupation (OCC) to affect both the intercept and the two growth rates, is defined by

$$\begin{aligned} b_{0i} &= b_0 + \gamma_{00}\, BW_i + \gamma_{01}\, OCC_i + u_{0i} \\ b_{1i} &= b_1 + \gamma_{11}\, OCC_i + u_{1i} \\ b_{2i} &= b_2 + \gamma_{21}\, OCC_i + u_{2i} \end{aligned} \quad (3)$$

where γ_{00} represents the effect of BW on the intercepts b_{0i}, γ_{01}, γ_{11} and γ_{21} represent the effects that OCC has on b_{0i}, b_{1i} and b_{2i}.

The equivalent model for BMI for subject i at age t, BMI_{it}, is defined as

$$BMI_{it} = c_{0i} + c_{1i}\, (t-2)\, (I_{t \leqslant 6}) + 4c_{1i}\, (I_{t > 6}) + v_{it} \quad (4)$$

where the notation is similar to the one used in equation (1), v_{it} are independent normal errors with mean zero and variance σ^2_v and (c_{0i}, c_{1i}) are specified as in (2).

Notice that values between $t = 6$ and $t = 7$ are taken to be constant because of the features of the data.