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PREDICTORS OF AGE AT MENARCHE IN THE NEWCASTLE THOUSAND FAMILIES STUDY

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Summary. Several studies have found relationships between early life factors (birth weight, length of gestation, height, weight, duration of breast-feeding, maternal age, social class, periods of infection, presence of adverse life events, and quality of housing conditions in childhood) and age at menarche but none has considered all of these factors in the same study. The follow-up study of the Newcastle Thousand Families birth cohort, established in 1947, provided age at menarche data collected retrospectively at age 50 from 276 women who returned self-completion questionnaires in 1997. Three main independent associations were observed: girls who experienced a shorter gestation, girls whose mothers were younger when they were born, and girls who were heavier at age 9 had earlier menarche. Birth weight, standardized for gestational age, was found to have different relationships with age at menarche depending upon how heavy or light a girl was at age 9. The results of this study support the hypotheses that conditions in fetal and early life are associated with the timing of menarche and that greater childhood growth is associated with earlier menarche. It is suggested that future work should focus on illuminating the mechanisms underlying these statistical relationships.

Introduction

Menarche, or the onset of menstruation, is an important outward and relatively late sign of maturity. Age at menarche is an important marker of reproductive maturation and has been shown to predict adult ovarian function (Apter, 1996; Windham *et al.*, 2002) and risk for diseases in adulthood including breast cancer (Apter *et al.*, 1989), rheumatoid arthritis (Karlson *et al.*, 2004) and low bone mass (Ito *et al.*, 1995). Previous studies have investigated associations between the timing of menarche and birth weight (Cooper *et al.*, 1996; Persson *et al.*, 1999; Adair, 2001; Romundstad *et al.*, 2003; dos Santos Silva *et al.*, 2004), prematurity (Bhargava *et al.*, 1995), birth order (Malina *et al.*, 1997; Apraiz, 1999; Padez, 2003), infant feeding practices (Novotny *et al.*, 2003), childhood adiposity (dos Santos Silva *et al.*, 2002; Anderson *et al.*, 2003; Ersoy *et al.*, 2004), acute and chronic illness (Khan *et al.*, 1996; Rosenstock *et al.*, 2000), stressful circumstances (Kim & Smith, 1998; Tahirovic, 1998) and socioeconomic status (Billewicz *et al.*, 1983; Chavarro *et al.*, 2004). However, these studies have produced inconsistent findings and have not considered all these factors in the same study population. The Thousand Families cohort provides an opportunity to test hypotheses linking these various aspects of health, social circumstances and growth in early life and timing of menarche. It is hypothesized, based on this previous research, that birth weight, birth order, childhood adiposity and socioeconomic status will be negatively correlated with age at menarche, while gestation length, duration of breast-feeding, experience of acute and chronic illness, and experience of stressful circumstances will be positively correlated with age at menarche.

Methods

The Thousand Families Study began as a prospective study of all 1142 children born in May and June 1947 to mothers resident in Newcastle-upon-Tyne, UK (Spence *et al.*, 1954). Participants were members of the cohort who were either traced through the NHS Central Register or contacted the study team in response to media publicity in preparation for a large-scale follow-up at age 50 years. Between October 1996 and December 1998, health and lifestyle questionnaires were sent out for completion and return. Of the original cohort, 832 (86% of the surviving sample of 967 children whose families remained in Newcastle for at least the first year of the study) were traced at age 49–51 (Lamont *et al.*, 1998).

Measurement of age at menarche

Age at menarche was collected retrospectively (in years and months) via the postal questionnaire when study participants were age 49–51. Recalled age at menarche in middle age can be unreliable and is best treated categorically (Cooper *et al.,* 2006). Thus participants were divided into three groups based on whether their menarche occurred early, average or late relative to other women in the study. The divisions were made with respect to difference from the sample mean. Those whose reported age at menarche was more than one standard deviation less than the mean age at menarche were placed in the early menarche group. Those whose reported age at menarche was more than one standard deviation greater than the mean age at menarche were placed in the late menarche group.

Measurement of early life experience

Information on early life was recorded prospectively for all study members and is described in detail elsewhere (Spence *et al.*, 1954; Miller *et al.*, 1960, 1974; Cooper *et al.*, 2006). Birth weights, as recorded by the midwife, were standardized for gestational age and sex (Freeman *et al.*, 1995). Socioeconomic status at birth was measured by paternal occupational social class and at age 5 years by that of the main wage earner in the household. Maternal age was collected at birth. Duration of breast-feeding was defined as the length of time an infant was at least partly breast-fed. Position in family at the time of birth was calculated from the number of older surviving siblings, including half-siblings. Housing conditions at birth and at age 5 years were scored for the presence of up to three or more of: overcrowding; lack of hot water; shared toilet; and dampness or poor repair. Experience of adverse life events in childhood (from birth to before their 9th birthday) was scored for the presence of up to three or more of: parental divorce or separation; death of a parent or sibling; parental incapacity through illness; serious illness of a sibling; serious debt; and parental criminal activity or cruelty. Illnesses were notified to the study team by the health visitors, parents, general practitioners, and from hospital referrals and attendances. The number of recorded episodes of infectious illness of various types from birth to age 8 years was used to calculate rates of respiratory infection and intestinal infection as well as an overall infection rate. Each of these rates is based on the number of episodes of infection recorded of the type specified from birth to the day before the 9th birthday divided by the number of complete years from birth to the day before the 9th birthday that each child was participating in the study. Rates of infection were not calculated for those participants who left the study in childhood before age 2, but returned for the age 50 follow-up. Height and weight at age 9 were collected prospectively by the school health service and converted to standard deviation scores relative to growth standards to adjust for skew and variations in age at measurement using the LMS method (Cole, 1990). Body mass index (BMI) was calculated from height and weight data as kg/m^2.

Statistical analysis

How representative participants in this study were in relation to the females in the original cohort were tested using χ^2 tests and t tests. Twins ($n=4$) were excluded from all analyses because of the differences in fetal development for multiple births and the fact that data contributed by co-twins are not independent.

Two variables to reflect change in weight and height in childhood up to age 9 were derived from the standardized residuals from linear regressions of standardized height and weight at age 9 years on standardized birth weight (Esrey *et al.*, 1990; Cameron *et al.*, 2005). Menarcheal age, presence of adverse life events, housing conditions, social class, and position in family were each treated as ordinal. For ordinal variables other than menarcheal age, adjoining categories were grouped together to avoid small numbers in certain categories. Other variables were treated as continuous.

Multivariable ordinal logistic regression with a probit link, appropriate for a dependent variable with polychotomous ordered categories created from an underlying continuous distribution, was used to investigate relations between explanatory variables and categorical age at menarche. Probit coefficients in logistic regression do not refer to the unit-for-unit change in the independent for the dependent variable but rather to the change in the cumulative normal probability of the independent variable per unit change in the dependent variable. The assumption of proportional odds was tested via the χ^2 test of parallel lines.

Interactions between variables representing indicators of fetal conditions and measures of childhood growth were investigated by centring the variables involved and multiplying the two dependent variables together. The derived variables were then entered into the regression model. In models containing interaction terms other predictor variables were also centred. Statistical assumptions were checked for validity for all regression models.

The statistical software package SPSS, version 12, was used for all statistical analyses.

Results

This sample differed significantly from the female non-twin members of the original cohort not included in this analysis in terms of birth weight ($t = -2{\cdot}4$, $p = 0{\cdot}017$), birth weight standardized for gestational age ($t = -2{\cdot}3$, $p = 0{\cdot}022$), social class at birth ($\chi^2 = 10{\cdot}7$, $p = 0{\cdot}005$) and position in family ($\chi^2 = 170{\cdot}1$, $p < 0{\cdot}001$). The cohort members for whom menarcheal age was available were heavier at birth, were less likely to be first births, and were more likely to be in social class III than the members of the cohort for whom data on menarcheal age are absent.

Mean reported menarcheal age for the participants was 12·94 ± 1·54 years, so participants who reported a menarcheal age below 11·41 years were considered to have early menarche ($n = 61$), average menarcheal age was considered to be between 11·41 and 14·48 years ($n = 165$), and late menarche was considered to be above 14·48 years ($n = 50$).

Descriptive statistics for all variables are given in Tables 1 and 2. Means and standard deviations are reported for normally distributed variables and medians and interquartile ranges otherwise.

Ordinal logistic regression results

The results of univariable ordinal logistic regression of age at menarche on continuous and categorical variables are presented in Tables 3 and 4 respectively. Standardized weight and BMI at age 9 years and change in weight between birth and age 9 were all found to be significant predictors of menarcheal age group with negative regression coefficients. While neither standardized nor unstandardized birth weight was associated with menarcheal age group, the association with length of gestation approached statistical significance. Excluding participants whose gestation was shorter than 37 weeks strengthened this relationship (Oprobit coefficient = 0·214, SE = 0·084, $p = 0{\cdot}011$). Maternal age at participant's birth was found to have a weak but significant positive association with menarcheal age. None of the other variables considered was associated with menarcheal age group.

The association between menarcheal age and length of gestation was found to be independent of standardized weight at age 9 in multivariable analysis (Oprobit coefficient = 0·119, SE = 0·086, $p = 0{\cdot}057$). The association between menarcheal age and maternal age at participant's birth was found to be independent of length of gestation (Oprobit coefficient = 0·025, SE = 0·11, $p = 0{\cdot}028$). However, the relationship between maternal age and menarcheal age was of reduced statistical significance when standardized weight at age 9 was entered into the model (Oprobit coefficient = 0·024, SE = 0·013, $p = 0{\cdot}062$).

Table 1. Descriptive statistics for continuous variables

Variable	*n*	Mean ± SD	Range
Birth weight standardized for gestational age and gender	276	0·05 ± 1·10	− 3·17–4·69
Unstandardized birth weight (kg)	276	3·39 ± 0·51	1·98–4·88
Standardized weight at age 9	214	− 0·53 ± 0·94	− 2·66–2·85
Standardized height at age 9	214	− 0·77 ± 1·11	− 3·48–3·56
BMI at age 9	214	16·41 ± 2·10	9·92–27·85
Childhood change in growth in height	214	0·00 ± 1·00	− 0·64–0·59
Childhood change in growth in weight	214	0·00 ± 1·00	− 0·82–0·59
		Median	Interquartile range
Length of gestation (weeks)	276	40·00	40–40
Maternal age at participant's birth	276	29	24–34
Duration of breast-feeding (days)	204	59·50	21·00–196·75
Respiratory infection rate (infections per year)[a]	274	1·00	0·67–1·44
Intestinal infection rate (infections per year)[a]	274	0·11	0·00–0·22
Overall infection rate (infections per year)[a]	274	1·67	0·11–2·11

[a] Rates are based on episodes of infection up to age 8 divided by the number of years from birth to age 8 that each child was participating in the study.

A significant interaction was found between standardized weight at age 9 and standardized birth weight on menarcheal age group ($p = 0{\cdot}030$). For girls born small for gestational age, weight for age at age 9 was not strongly associated with age at menarche. However, for girls born large, weight for age at 9 was more strongly associated with menarcheal age. The girls who were the youngest at menarche were born heavy for their gestational age and were heavy for their age at 9. The girls who had the latest menarche were also born heavy for their gestational age but were light for their age at 9.

Discussion

Principal findings

The age at menarche as recalled for this cohort (mean 12·94 years, median 13·00 years) was a few months earlier than found in cross-sectional studies of menarcheal ages for girls born in the north-east of England in the following few decades of the twentieth century. Studies of girls in Newcastle-upon-Tyne, Northumberland and South Shields found median ages at menarche of 13·3, 13·3 and 13·4 years respectively (Billewicz *et al.,* 1981; Roberts *et al.*, 1971, 1975). These small differences in median menarcheal ages may be due to systematic error in recall in the Thousand Families data, random variation or cohort effects for different birth years.

Table 2. Descriptive statistics for categorical and ordinal variables

Variable	*n* (%)
Social class at birth (*n*=273)	
I & II	24 (8·8)
III	179 (65·6)
IV & V	70 (25·3)
Social class at age 5 (*n*=276)	
I & II	18 (7·5)
III	134 (55·8)
IV & V	88 (36·7)
Housing conditions at birth (*n*=276)	
0	124 (44·9)
1	76 (27·5)
≥2	76 (27·5)
Housing conditions at age 5 (*n*=249)	
0	129 (51·8)
1	70 (28·1)
≥2	50 (20·1)
Order of birth in family (*n*=276)	
1st surviving child	134 (48·6)
2nd surviving child	74 (26·8)
3rd or higher surviving child	68 (24·6)
Number of adverse life events (*n*=236)	
0	127 (53·8)
1	55 (23·3)
2	23 (9·7)
≥3	31 (13·1)

This analysis, using data from a longitudinal cohort study, found that girls who experienced a shorter gestation and girls who were heavier at age 9 years had earlier menarche, as hypothesized. A relationship that was found, though not hypothesized, was that girls whose mothers were older when they were born experienced later menarche. This was explored as a potential association because of the influence of maternal age on the fetal environment. Birth weight, standardized for gestational age, was found to have different relationships with age at menarche depending upon the girl's standardized weight at age 9. Girls with relatively high birth weights for gestational age who also had high weights at age 9 years tended to be younger at menarche. Contrary to these hypotheses, timing of menarche was not associated with rate of infection, presence of adverse life events, the duration of breast-feeding, or socioeconomic indicators.

Table 3. Predictors by menarcheal age category; mean ± standard deviation and ordinal logistic regression results

Variable	*n*	Mean ± SD			Oprobit coeff.	95% CI	*p* value
		Early menarche group (<11·4 years)	Average menarche group (11·41–14·48 years)	Late menarche group (>14·49 years)			
Birth weight standardized for gestational age	276	0·11 ± 1·27	0·02 ± 1·07	0·05 ± 1·00	−0·020	−0·14, 0·10	0·746
Birth weight (kg)	276	3·35 ± 0·57	3·39 ± 0·52	3·42 ± 0·43	0·094	−0·17, 0·36	0·481
Gestation length (weeks)	276	39·52 ± 1·62	39·85 ± 1·15	39·98 ± 1·24	0·106	−0·00, 0·22	0·055
Standardized weight at age 9	214	−0·24 ± 1·04	−0·51 ± 0·92	−0·93 ± 0·71	−0·295	−0·46, −0·13	0·001
Standardized height at age 9	214	−0·60 ± 1·07	−0·78 ± 1·11	−0·95 ± 1·16	−0·106	−0·24, 0·03	0·131
BMI at 9	214	17·01 ± 2·51	16·45 ± 2·01	15·53 ± 1·53	−0·127	−0·20, −0·05	0·001
Maternal age at participant's birth	276	28·02 ± 6·02	29·07 ± 5·91	30·54 ± 6·36	0·025	0·003, 0·047	0·029
Duration of breast-feeding (days)	204	115·24 ± 118·24	113·51 ± 119·16	110·5 ± 107·23	<0·001	−0·00, 0·00	0·860
Respiratory infection rate (infections per year)[a]	274	1·27 ± 0·89	1·08 ± 0·63	1·30 ± 0·91	0·008	−0·17, 0·19	0·933
Intestinal infection rate (infections per year)[a]	274	0·14 ± 0·14	0·15 ± 0·20	0·15 ± 0·21	0·091	−0·61, 0·79	0·799
Overall infection rate (infections per year)[a]	274	1·93 ± 1·01	1·64 ± 0·86	1·87 ± 0·95	−0·040	−0·19, 0·11	0·590
Childhood change in growth in height	214	0·14 ± 0·97	−0·00 ± 0·99	−0·17 ± 1·06	−0·115	−0·27, 0·04	0·141
Childhood change in growth in weight	214	0·30 ± 1·10	0·02 ± 0·98	−0·43 ± 0·78	−0·276	−0·43, −0·12	0·001

[a] Rates are based on episodes of infection up to age 8 over the number of years from birth to age 8 that each child was participating in the study.

Table 4. Categorical variables as predictors of timing of menarche

Variable	Categories	*n*	Mean ± SD	Oprobit coeff.	95% CI	*p* value
Social class in 1947	I & II	24	13·17 ± 1·34	0·155	− 0·37, 0·68	0·562
	III	179	13·03 ± 1·58	0·219	− 0·09, 0·53	0·170
	IV & V	70	12·62 ± 1·52	—		—
	Model	273	12·94 ± 1·55	—	—	0·390
Social class in 1952	I & II	18	12·83 ± 1·17	0·042	− 0·53, 0·62	0·887
	III	134	13·15 ± 1·51	0·014	− 0·29, 0·32	0·927
	IV & V	88	12·88 ± 1·54	—	—	—
	Model	240	13·03 ± 1·50	0·042	—	0·989
Housing conditions at birth	0	124	13·01 ± 1·47	0·008	− 0·32, 0·33	0·963
	1	76	12·94 ± 1·52	0·070	− 0·29, 0·43	0·700
	≥ 2	76	12·85 ± 1·68	—	—	—
	Model	276	12·94 ± 1·54	—	—	0·910
Housing conditions at age 5	0	129	13·09 ± 1·40	0·168	− 0·20, 0·54	0·375
	1	70	13·09 ± 1·48	0·156	− 0·26, 0·57	0·458
	≥ 2	50	12·62 ± 1·77	—	—	—
	Model	249	12·99 ± 1·51	—	—	0·658
Order of birth in family	1st	134	12·77 ± 1·55	− 0·320	− 0·65, 0·01	0·059
	2nd	74	13·01 ± 1·48	− 0·181	− 0·55, 0·19	0·342
	3rd or higher	68	13·23 ± 1·56	—	—	—
	Model	276	12·94 ± 1·54	—	—	0·163
Number of adverse life events	0	127	13·02 ± 1·50	− 0·147	− 0·593	0·299
	1	55	13·05 ± 1·34	− 0·151	− 0·651	0·348
	2	23	12·78 ± 1·51	− 0·118	− 0·730	0·494
	≥ 3	31	13·31 ± 1·79	—	—	—
	Model	236	13·04 ± 1·50	—	—	0·929

Comparisons with other studies

This study's findings contrast with those of several studies that have found associations between menarcheal age and birth weight (Romundstad *et al.*, 2003), quintiles of birth weight (Cooper *et al.*, 1996), and birth weight standardized for gestational age (Persson *et al.*, 1999; Romundstad *et al.*, 2003). In several cases, the authors were able to test whether the associations between birth characteristics and menarcheal age were mediated or modulated by postnatal growth. Two of these studies found that the associations initially found between small size at birth and early menarche could be accounted for by greater early childhood growth in girls born small for gestational age (Persson *et al.*, 1999; dos Santos Silva *et al.*, 2002).

Cooper *et al.* (1996) observed that those girls with the youngest age at menarche had low birth weights and were heavy at age 9 and those who were oldest at menarche were heavy at birth and lighter at age 9. This is somewhat different from the results of the present study, which indicate that while girls who were small for gestational age (SGA) and were heavy for their age at 9 reached menarche before their SGA peers who were lighter at age 9, the girls who were larger for gestational age and were heavy for their age at 9 also had early menarche, even earlier than that of SGA girls.

Though length of gestation has not been a primary focus of the studies of the effects of fetal conditions on later health and development, the finding of an association between shorter gestation and early menarche that appears to be independent of later growth has been seen previously in at least one other prospective study (Adair, 2001). In addition, a further study comparing premature infants and controls for indices of growth and maturation found a significant relationship between length of gestation and age at menarche (Bhargava *et al.*, 1995), in the same direction as in the current study. However, a lack of an association between prematurity and the timing of menarche has also been reported previously (Persson *et al.*, 1999). The potential mechanisms for such an association are unclear. It is possible that the relationship between age at menarche and gestation length may be due to the effect of *in utero* hormonal exposure on the 'set point' of the negative feedback loop of the hypothalamic-pituitary-ovarian (HPO) axis or the effect of an *in utero* exogenous chemical exposure on this 'set point'. However, the influence of independent factors affecting the pace and/or magnitude of fetal and childhood growth and development cannot be ruled out.

One previous study has reported a significant association between menarcheal age and an interaction between maternal age and leptin genotype (Comings *et al.*, 2001). Neither variable showed a significant association with menarcheal age, though the authors state that this was due to an association cross-over effect in which the relationship for those participants whose maternal age was below age 30 was in the opposing direction to that of participants whose maternal age was 30 years or over. Other studies have found significant relationships between advanced maternal age and reduced fecundity in female offspring (Smits *et al.*, 1999; Smits *et al.*, 2002), which is consistent with our finding that later maternal age is associated with later menarche, as later menarche is associated with reduced ovulatory frequency throughout the reproductive lifespan (Wallace *et al.*, 1978; Vihko and Apter, 1984; Apter *et al.*, 1989). These associations may be due to 'oocyte overripeness' as a result of longer menstrual cycles in older women (Smits *et al.*, 1995), to accumulated damage to oocytes in older women (Volarcik *et al.*, 1998), possibly via oxidative phosphorylation (Wilding *et al.*, 2005), or to differences in reproductive hormone levels in older women (Wang & vom Saal, 2000).

The lack of associations between age at menarche and birth order and childhood socioeconomic status is consistent with findings in other areas of the north-east of England for a similar time period to that covered by the Thousand Families Study (Roberts *et al.*, 1971, 1975). However, a previous study of girls born in Newcastle-upon-Tyne in 1962 did find significant associations between both birth order and socioeconomic status and menarcheal age (Billewicz *et al.*, 1983). It is possible that socioeconomic status effects were relatively small in this cohort as a result of post-war rationing (Prynne *et al.*, 1999; Wright & Parker, 2004). Studies outside of the North of England considering the potential relationship between socioeconomic status and age at menarche have reported inconsistent findings (Bielicki *et al.*, 1986; Chavarro *et al.*, 2004; Ersoy *et al.*, 2004).

Unlike this study's findings, later menarche has previously been reported to be associated with increased rates of infection in early childhood (Khan *et al.*, 1996). However, differences in both the method of calculating rates and the types and burden of infections and external circumstances contributing to such rates may account for this discrepancy. Khan *et al.*'s nutritional intervention study of Guatemalan girls calculated percentages of time spent ill with diarrhoea and respiratory illnesses in the study period (Khan *et al.*, 1996), whereas our study used number of illness periods per year. The amount of time ill may be a more accurate way of assessing the burden of illness on development. Differences in nutrition, sanitation and access to health care between rural Guatemala and Newcastle-upon-Tyne in the twentieth century and the nutritional intervention itself are likely to have influenced infection rates in children.

The strong association between childhood weight and BMI and menarcheal age that was found in this study is consistent with previous research (Cooper *et al.*, 1996; Adair, 2001; dos Santos Silva *et al.*, 2002; Anderson *et al.*, 2003; Ersoy *et al.*, 2004). There are several plausible explanations for this association, including direct effects of fat on the HPO axis (such as aromatization of androgens into oestrogens) and direct effects of the maturation of the HPO axis on fatness (via oestrogens promoting fat storage) (Nimrod & Ryan, 1975).

The lack of association between menarcheal age and each of the height-related variables does not support the hypothesis that height in childhood is a predictor of menarcheal age. Using data from the UK MRC NSHD cohort, Cooper *et al.* (1996) found an inverse association between height at age 7 and menarcheal age among girls who had reached menarche before age 15 but did not find this relationship in a model which included all participants. Later analyses of childhood growth trajectories in the same cohort found that change in ranks of height in infancy and childhood were positively associated with age at menarche (dos Santos Silva *et al.*, 2002), which suggests that height velocity may be the important factor, as suggested by Ellison (1981a, b).

Strengths and limitations

The study sample differed from the remainder of the females in the original cohort in some characteristics of early life. However, inclusion of cohort members who had moved out of the study region increased the representativeness of the population studied. Experiencing childhood in the immediate post-war environment, including rationing of food, may have resulted in reduced dietary variability compared with later cohorts.

All data except menarcheal age were collected prospectively. More complete multiple measures of weight and height in childhood would have allowed a clearer examination of the potential influence of the rate of growth relative to the starting point of each child on menarcheal age.

Conclusion

This study lends some support to the hypotheses that reproductive maturation is responsive either to the childhood circumstances that promote or delay growth or to growth in childhood itself. The hypothesis that fetal conditions are associated with the timing of menarche is somewhat supported, but not confirmed by the data. Future research should be oriented to unpicking the causes of individual and population variation in rate of growth *in utero* and variation in length of gestation with a specific view to understanding the mechanism underlying associations between reproductive maturation and fetal conditions.

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