Determinants of Age at Menarche in the Newcastle Thousand Families Study

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ABSTRACT

Early life determinants of age at menarche were investigated for female participants in the longitudinal Thousand Families Study based in Newcastle upon Tyne. Age at menarche was collected retrospectively from 276 participants at the age 50 follow-up in 1997. Birth weight, length of gestation, height, weight, duration of breast feeding, social class, periods of infection, and quality of housing conditions in childhood were collected prospectively. Ordinal logistic regression was used to test univariate and multivariable associations of fetal and childhood data with menarcheal age group membership. Separation into 3 menarcheal age groups was made with respect to distance in standard deviations from the sample mean: early (μ->1 SD), middle ($\mu\pm$<1 SD), late (μ+>1 SD). Regression models were also used to test univariate and multivariable associations between fetal and childhood data and age at menarche as a continuous variable. Two main independent associations were observed: girls who experienced a shorter gestation and girls who were heavier at age 9 had earlier menarche. Birth weight adjusted 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 hypothesis that fetal conditions are associated with the timing of menarche and the hypothesis that greater childhood tissue growth is associated with earlier menarche. It is suggested that future work should focus on illuminating the mechanisms underlying these statistical relationships.

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DECLARATION

The analyses in the appendix of this thesis have been submitted for publication in the International Journal of Epidemiology, under the title 'The validity of age at menarche self-reported in adulthood ' and authorship Rachel Cooper, Mwenza Blell, Rebecca Hardy, Stephanie Black, Tessa M Pollard, Michael EJ Wadsworth, Mark S Pearce and Diana Kuh. Rachel Cooper and Mwenza Blell planned and ran the analyses with supervision from Rachel Hardy, Diana Kuh, Stephanie Black, Tessa M Pollard and Mark S Pearce. Rachel Cooper with input from Mwenza Blell drafted the paper and all authors commented on this and contributed to the final version. All other material included is a result of my own work and has not been submitted by me for publication or for a degree in this or any other university. In all cases, material from others is acknowledged and quotations suitably indicated.

STATEMENT OF COPYRIGHT

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INTRODUCTION

Menarche, or the onset of menstruation, is an important outward and relatively late sign of maturity in human females. It is preceded by other indicators of sexual maturation: adrenarche (maturation of the adrenal cortex that results in greater production of androgens), pubarche (beginning of puberty indicated by the appearance of pubic hair), and the first stages of thelarche (breast development). Age at menarche is an important marker of reproductive maturation and has been shown to predict adult ovarian function (Apter, Reinila, and Vihko 1989; Apter 1996; Windham et al 2002). Menarche also has important sociocultural meanings in certain contexts, where it may signal a girl's suitability for marriage, readiness for initiation ceremonies, or that she has 'become a woman' (Winslow 1980; Fricke, Syed, and Smith 1986). Understanding the influences on the timing of menarche for individuals and the species may yield important information for the tracking of changes in the rate of development world wide, because of its implications for adult morbidity and mortality, and for understanding what evolutionary pressures have shaped the reproductive system of the human female. Menarche is a result of the progressive desensitization of the negative feedback loop of the hypothalamic-pituitary-ovarian (HPO) axis, this desensitization leads to a rise in steroid levels and menarche occurs when steroids reach a level high enough to stimulate endometrial proliferation. Many factors have been suggested to influence or even trigger this desensitization.

I. Variation in Age at Menarche

Age at menarche varies greatly between individuals and between populations (Parent et al 2003). Age at menarche in individuals varies from eight years of age (Herman-Giddens et al 1997) to nineteen or twenty years of age (Madrigal 1991; Graham et al 1999). The age limits of "normal" menarche are not clear. Comparing individuals within a population as well as population subgroups has shown variation in age at menarche on the order of months or years (e.g. Khan et al 1996; Ersoy et al 2004, Leenstra et al 2004; Vitalle et al 2003). Variation in population means have also been well documented for over a century (Parent et al 2003). There have been many studies of the phenomena of a general reduction in age at menarche known as the secular trend. The secular trend has been documented in various countries around

the world (Eveleth and Tanner 1990; Parent et al 2003). Increases in overall socioeconomic status are usually cited as the reason for the decreased age at menarche seen in the groups studied (Wyshak and Frisch 1982; Graham et al 1999; Tanner 1973; Okasha et al 2001). Outside Europe, Australia, and North America the secular trend began somewhat later and in some places has proceeded at a considerably faster rate than previously observed. While some studies suggest that the secular trend has stopped in Europe in recent years (Helm and Grolund 1998; Whincup et al 2001), others suggest that age at menarche is continuing to decline (Olesen, Jeune, and Boldsen 2000).

II. Genetic Determinants of Age at Menarche

The question of whether the timing of menarche is under genetic control is an important one. Considering the worldwide observation of the secular trend in age at menarche and its association with improved conditions (rather than intense selective pressure), the timing of menarche is not likely to be wholly under genetic control. Many studies have attempted to assess the genetic component (heritability, h2) of age at menarche. Most of these have used mother-daughter correlations and twin and non-twin sister-sister correlations. In no less than 20 papers since 1926, correlation coefficients have been reported for these relationships (Salces et al 2001; Ersoy et al 2005). Correlation coefficients for mother-daughter menarche comparisons range from 0.15 to 0.54 (Salces et al 2001). Correlation coefficients for sister-sister comparisons range from 0.28 to 0.61 (Salces et al 2001). Ersoy et al (2005) note that the mother's age at menarche fails to be a good predictor of daughter's age at menarche when the daughter is obese. Towne et al (2005) use data from the Fels Longitudinal Study to calculate the heritability of age at menarche. The Fels Longitudinal Study has information on age at menarche for participants as well as age at menarche for many different family members spanning several generations (Towne et al 2005). The authors report that about half of the observed phenotypic variance is due to genetic effects (h2 = 0.49 ± 0.13; 95% CI of h2: 0.24-0.73) (Towne et al 2005). However, comparisons of close family members who have shared a social and physical environment would seem to introduce confounders to this method of assessing the genetic component of menarcheal age.

Studies using two different mathematical approaches have also strengthened the idea that in the determination of age at menarche genetics plays a significant role (Treolar and Martin 1990; Meyer et al 1991). Treolar and Martin (1990) studied 1177 pairs of monozygotic twins and 711 pairs of dizigotic twins and concluded that nonadditive genetic variance (epistasis, more complex multi gene interactions involving dominance) played an important role in age at menarche. Meyer and colleagues (1991) came to the same conclusion through a similar study design. Kaprio et al (1995) determined that 74% of the variance in age at menarche was due to genetic factors and 26% due to environmental effects. This finding accords with Treolar and Martin's (1990) idea that the genetic effect on age at menarche is increased relative to environmental effects in privileged countries. Kaprio et al (1995) also note that there is a strong correlation ($r = 0.57$) between additive genetic effects on age at menarche and those on body mass index which indicates a large amount of common genetic effects. Treolar and Martin (1990) also state that menarche shows a pattern of genetic variance typical of a fitness trait. Stavrou et al (2002) suggest the *Xba*I polymorphism, and possibly *Pvu*II on the estrogen receptor gene as genetic determinants of age at menarche. Xita et al (2005) found an association between the timing menarche and the number of tandem repeats in an allele for a promoter of the gene for sex hormone binding globulin (SHBG). As there is general agreement that the timing of menarche is not under complete genetic control, the question remains, what developmental influences determine the rest of variation in age at menarche?

III. Developmental Determinants of Age at Menarche

A. Environmental Exposures

There is evidence from a number of studies that age at menarche is affected by certain, possibly common, chemical exposures during prenatal and childhood development. Potential evidence for effects on menarche of common exposures *in utero* and childhood comes from a California study of 994 females (Windham et al 2004). This study found an association between mothers' tea-drinking in pregnancy and later menarche, parental smoking in pregnancy and earlier menarche, parental smoking both in pregnancy and childhood and earlier menarche, and little effect of

mothers' alcohol intake and no effect of mothers' intake of coffee on age at menarche (Windham et al 2004).

A small Belgian study comparing Belgian children, foreign adopted, and foreign non –adopted girls with precocious puberty (defined in the study as achievement of Tanner Breast Stage 2 before age 8) found that 21 out of 26 foreign children with precocious puberty had detectable concentrations of p,p'-DDE (dichlorodiphenyldichloroethylene), which is derived from the organochlorine pesticide DDT (dichlorodiphenyltrichloroethane) however only 2 out of the 15 Belgian children with precocious puberty had detectable p,p'-DDE concentrations though it is not known how many were exposed to DDT or when (Krstevska-Konstantinova et al 2001). Several other studies have found correlations between premature thelarche and exposure to various endocrine disrupting chemicals, but their results have been less convincing (Freni-Titulaer et al 1986; Scaglioni et al 1978; Fara 1979; Saenz de Rodriguez et al 1985; Kimball et al 1981; Colon et al 2000).

In a study of 138 Akwesasne Mohawk girls in Canada, a logistic regression analysis indicated that increasing levels of lead and levels of a group of four E-PCBs (estrogenic polychlorinated biphenyls) were associated with decreasing and increasing likelihood of attaining menarche respectively (Denham et al 2005). These associations remained significant after controlling for age, SES, and other detected toxicant levels. Higher E-PCB levels were associated with a greater likelihood of having reached menarche (β=2.13, SE= 1.017, p= 0.04). Lead levels above the median were associated with a 10.6 month delay in menarche (β= -1.29, SE= 0.494, p= 0.01) (Denham et al 2005). Denham et al (2005) report that PCB levels among the study participants are consistent with "a cumulative, continuing exposure pattern" (p. e27). The study failed to detect a relationship between menarche and p,p'-DDE, mirex, mercury, nor HCB (hexachlorobenzene) levels (Denham et al 2005).

Two studies from Michigan USA indicate that exposure to organochlorines *in utero* or through breastfeeding may affect the timing of menarche. Vasiliu, Muttineni, and Karmaus (2004) used known maternal serum PCB and DDE levels to extrapolate levels during pregnancy and correlated this with retrospectively collected age at

menarche of their offspring (n=151). *In utero* exposure to DDE lowered age at menarche by one year per 15 micro g/L however maternal PCB exposure was not associated with menarche (Vasiliu, Muttineni, and Karmaus 2004). When estimated body size at menarche was controlled for on a subsample of women (n=102) the association with DDE exposure was no longer significant. Another Michigan study extrapolated from previously measured maternal serum polybrominated biphenyl (PBB) levels to levels during pregnancy and breastfeeding of 327 female offspring using a model of PBB decay (Blanck et al 2000). This study found that girls exposed to high levels PBB *in utero* (defined as ≥ 7 parts per billion) who were breastfed had earlier menarche than girls who were not breastfed and girls who were exposed to lower levels *in utero* (Blanck et al 2000). This study also found an association between perinatal PBB exposure and early attainment of pubic hair stages.

In a study in two rural counties in China, later age at menarche was associated with non-endocrine disrupting pesticide exposure before age at menarche, whereas exposure to endocrine disrupting pesticides was found to have no effect after all confounders were controlled for (Graham, Larsen, and Xu 1999). The authors admit to potential problems with the results because 33% of women exposed to pesticides chose "Other" pesticide rather than a type known to be endocrine disrupting or non-endocrine disrupting (Graham, Larsen, and Xu 1999).

Krstevska-Konstantinova and colleagues (2001) put forward two explanations regarding the connection between altered timing of puberty and estrogenic endocrine disrupting pesticides. The first explanation suggests that the estrogenic compounds weakly stimulate the hypothalamus and other estrogen sensitive tissues promoting maturation of the hypothalamic-pituitary-ovarian axis and perhaps directly triggering thelarche (Krstevska-Konstantinova et al 2001). The second, the withdrawal hypothesis, suggests that during exposure these compounds provide negative feedback on the HPO axis and could delay puberty if exposure is high and continued (Krstevska-Konstantinova et al 2001). Once this exposure is removed, however, the axis, having become desensitized by the prior high levels providing negative feedback, matures at an accelerated rate (Krstevska-Konstantinova et al 2001).

B. Growth as a Determinant of Age at Menarche

Childhood and adolescent growth are generally assessed through the use of height and weight measures. These are often used to calculate growth velocities or used in association with global, regional, or national references of weight for height, weight for age, and height for age centiles or *z*-scores (Rogol, Clark, and Roemmich 2000). Use of global or US references on various populations of children has been questioned as these references may be biased by the inclusion of children from more affluent countries with higher levels of adiposity. However, growth references are considered useful for indicating the lower or higher probability that a child is growing healthily. Generally, height is considered to primarily reflect skeletal growth, weight is considered to primarily reflect tissue growth. Factors considered to influence growth in childhood include genetics, nutrition (level of energy intake), physical activity (level of energy expenditure), and burden of disease (affecting both level of energy intake and energy expenditure). Wasting (very low weight for height) in children has been found to be more reversible than stunting (very low height for age) (Martorell, Khan, and Schroeder 1994; Golden 1994). However, these are not mutually exclusive conditions and wasted children are also sometimes stunted and vice versa (Waterlow 1972; Martorell, Mendoza, Castillo 1988). Skinfold measurements and bioelectrical impedance can provide a direct indication of the level of adiposity. Skinfold measurement, while somewhat unreliable, is cheaper and be used to distinguish between central adiposity (higher proportion of fat in the trunk) and overall adiposity (Wells and Victora 2005).

Critical Weight/Levels of Fat as a Determinant of Age at Menarche

In upwards of twenty publications since the 1970s Rose Frisch and colleagues have discussed a "critical weight" or "critical fat" hypothesis for determination of age at menarche. This hypothesis was developed as an explanation of the delay in menarche seen in women involved in very physically demanding activity and was further tested on rats. Frisch and Revelle (1970) initially published material supporting a hypothesis that there was critical weight of 47.8 kg for menarche regardless of height. Crawford and Osler (1975) attempted to test this hypothesis and found weight to be a poor predictor as taller girls exceeded the 47.8 kg "critical" weight before the onset of menses. Their results indicated that body composition was a better predictor of menarcheal status and suggest that gonadotropins play a greater role than indicated in Frisch and Revelle's hypothesis (Crawford and Osler 1975). By 1974, Frisch and

MacArthur had revised the hypothesis and instead proposed a minimum ratio of fat to lean mass (equal to 17% body fat) required for menarche in human females, calling this level a necessary but not a sufficient requirement. Richardson et al (1983) conducted a study on 4390 girls in South Africa and found girls who had not achieved menarche with percentages of body fat well above the 17% critical level, and moreover in many pre-menarcheal girls the percentage of body fat was greater than the 22% level proposed by Frisch for regular ovulation. Tsuzaki et al (1989) in a study that combines data from 14 retrospective studies done over 50 years, a sample size of some 17,000 girls, find mean height and weight at menarche to be highly variable while age at menarche continually declined.

While numerous studies have found a correlation between several anthropometric indices of tissue growth and menarche (see below), serious criticisms have been levelled at the hypothesis proposed by Frisch and colleagues in its various incarnations. Johnston et al (1975) point out that in eight samples, there was a 71.4 kg range in weights at which menarche was achieved, asserting that the critical weight of 47-48 kg does not appear to apply to individuals. Johnston et al (1975) also show that girls with earlier menarche appear to be heavier at menarche than girls who reach menarche later when adjustment for height is done. Scott and Johnston (1982) criticise Frisch and colleagues' use of estimates of fatness based on height and weight which Scott and Johnston cite as having been shown to be "intolerably erroneous" for use in individuals. Scott and Johnston (1982) also cite examples of exceptions such as those mentioned here where many individuals above and below the suggested threshold do not conform to expectations of the presence or absence of menarche.

Cameron (1976) points out that a threshold should be identifiable by the reduction in parameter variance as it is approached. The presence of this reduction in variance can help to distinguish the relationship from a correlation. Ellison (1981a) uses longitudinal data previously used by Frisch and Revelle in the original demonstration of their hypothesis to show that none of the suggested variables (weight, total body water, and weight for height) show the pattern of decreasing variance approaching menarche. Ellison (1981a) shows that height, however, does show this pattern of decreasing variance approaching menarche. Cameron's (1976) results from

longitudinal studies of British girls that include skinfold measurements and weight also show no reduction in variance as menarche is approached. Ellison (1990) also points out that when the original data used by Frisch and Revelle to develop their hypothesis are plotted, the relationship between weight at menarche and age at menarche is "virtually a textbook example of a zero correlation (p.939) and the R^2 of that plotted relationship is 0.003. Ellison (1990) plots a wholly unrelated variable (ordinal position of subjects in original data collection) against age at menarche to show that it has virtually the same relationship to age at menarche as does weight (graphs very similar and R^2= 0.001). Ellison further points out that Frisch and Revelle then use these data in an analysis of variance which he calls inappropriate for two continuous variables. Billewicz, Fellowes and Hytten (1976) use data from 2 Frisch papers to question their conclusions. Billewicz, Fellowes and Hytten (1976) cite several reasons that Frisch's conclusions that menarche is triggered by a critical body weight (unrelated to age) are unacceptable. One reason is that variation in body weight in the data used by Frisch is as great among menstruating as non-menstruating girls (Billewicz, Fellowes and Hytten 1976). A second reason is that the likelihood of having attained menarche for a given weight increases with age in the data (Billewicz, Fellowes and Hytten 1976). A third reason is that there is a trend for increasing weight at menarche of participants with increasing age (Billewicz, Fellowes and Hytten 1976). A fourth reason is that less than half (41%) of girls started to menstruate at the critical weight of 48 +/- .5 kg (Billewicz, Fellowes and Hytten 1976). Garn, LaVelle and Pilkington (1983) collected triceps and subscapular skinfold measurements from 2251 pre and post-menarcheal girls to determine whether they could detect a critical level of fatness below which menarche was not found. The authors could not identify such a critical level whether they considered skinfold measurements alone or used them to calculate a percentage of body fat for the participants (Garn, LaVelle and Pilkington 1983). While some girls with skinfold thickness of 25 mm had not experienced menarche, other girls with skinfold thickness of only 5 mm had reached menarche (Garn, LaVelle and Pilkington 1983).

Frisch (1996) has developed her hypothesis further to include a mechanism by which fatness has an effect on gonadotropins by implicating the protein leptin, discovered in 1995 by Halaas and colleagues, which is suggested to signal the hypothalamus information about whether fat stores in the body have reached critical levels leading

to a reduced or increased response to gonadotropin releasing hormone (GnRH) which leads to reduced or increased production of gonadotropins, which are responsible for the synthesis of estrogen. However, the much criticised suggestion that a specific level of fat is permissive of menarche is still at the core of the revised hypothesis.

Intrauterine Growth

David Barker and colleagues (see Barker et al 1989, 2002; Barker 1994, 2004 etc.) have shown that intrauterine growth retardation predisposes one to risk for cardiovascular disease and diabetes. This in addition to findings that both age at menarche (Kelsey 1993; Peeters et al 1995) and birth weight (Michels et al 1996; Vatten et al 2005; Innes, Byers, and Schymura 2000) appear to influence risk of developing breast cancer, has spurred epidemiologists and others on to investigate markers of intrauterine growth for associations with timing of menarche. These associations with breast cancer, however, seem to be independent of one another (dos Santos Silva et al 2004; Romundstad et al 2003). There is some question as to whether the measures taken as indicators of intrauterine growth (birth weight, ponderal index, fetal to placenta ratio, birth weight adjusted for gestational age) adequately represent the fetal nutritional environment or whether cut-off points of such measures used to divide those considered to have experienced intrauterine growth retardation from normal infant girls are somewhat arbitrary (Koziel and Jankowska 2002; Mitchell 2001; Fay et al 1991; Godfrey and Barker 2001).

However, there is some evidence from these indicators that there are very early developmental determinants of age at menarche. Several studies have used raw birth weight as a predictor of menarche. Ibanez and colleagues (2000) found that Catalan girls with low birth weights achieved menarche 1.6 years before the normal birth weight group (11.9 ± 0.3 years vs. 12.9 ± 0.2 years). Hack et al (2003) report the finding of a slightly later age at menarche in girls born with very low birth weight (VLBW) but do not report whether this difference was significant. However, Stark et al (1989) using data from the National Child Development Study (1958 UK cohort) were not able to detect an effect of birth weight on menarche. A follow-up study of 137 low birth weight babies (less than 2000 g) showed that, compared to controls, low birth weight girls experienced a 6 month delay in menarche (Fledelius 1982). Similarly, a Czech study found that low birth weight girls (less than 2500 g)

experienced a 3-6 month delay in menarche (Berankova 1997). However, a small German study found no statistically significant association between birth weight group (birth weight below 1500 g, 1500-2000 g, and 2001-2500g) and menarcheal age (Enzelsberger, Eppel, and Grunberger 1987). This German study, however, had a sample size of 50, only compared groups of low birth weight girls to one another, and reduced its statistical power by using three groups rather than two and by using birth weight as a categorical rather than continuous variable.

In two papers links between birth weight and menarcheal age in the Medical Research Council National Survey of Health and Development (MRC NSHD) cohort have been investigated (Cooper et al 1996; dos Santos Silva et al 2002). The MRC NSHD does not have prospective menarcheal ages for participants who experienced menarche after their interview between July 1960 and July 1961, when the cohort was a mean age of 14.5 years, when the data collection period that included menarche questions ended (Cooper et al 1996; dos Santos Silva; appendix). In all analyses, quintiles of the distribution of birth weight used (Cooper et al 1996; dos Santos Silva). Cooper et al (1996) performed analyses in two ways. In one set of analyses, girls with known ages at menarche were included in univariate analysis of associations with quintiles of birth weight, no significant association was found (Cooper et al 1996). However, when adjusted for relative weight at age 7, the relationship between birth weight and age at menarche became significant (Cooper et al 1996). In the second set of analyses a Weibull survival model was used to allow inclusion of individuals whose menarche occurred after the data collection period (Cooper et al 1996). Univariate analysis revealed a significant association between birth weight and age at menarche and multivariable analysis showed that this relationship remained significant when relative weight at age 7 was controlled (Cooper et al 1996). Cooper et al (1996) state 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. Reanalysis of data from the same cohort however, showed that when growth in infancy was controlled the relationship reversed and those girls born heavier reached menarche earlier than those born lighter (dos Santos Silva et al 2002).

In the Cebu Longitudinal Health and Nutrition Survey (CLHNS), age at menarche was found to be predicted best by size at birth rather than birth weight (Adair 2001). Girls who were born long and thin achieved menarche before girls born short and light (Adair 2001). The effect of thinness at birth was greatest for girls who grew faster in the first six months of life (Adair 2001). These effects remained statistically significant when pre-menarcheal BMI and skinfold thickness were held constant. Thinness at birth has also been implicated by a Norwegian study of 3343 girls which found a significant trend for earlier menarche with decreasing birth weight and with low ponderal index (thinness at birth, calculated by dividing birth weight by birth length cubed) (Romundstad et al 2003).

Some researchers (Godfrey and Barker 2001) have implicated poor maternal nutrition as the factor that leads to the effects seen in later life among smaller babies, however, a Dutch study looking that effects of famine during pregnancy on fertility and maturation found no effect of *in utero* exposure to famine on menarcheal age though the famine was shown to have affected fetal growth (Lumey and Stein 1997).

Birth weight is asserted to be the result of the rate of growth during gestation and the gestational age at delivery (Leon et al 1998). Some researchers have attempted to investigate the effects of length of gestation and fetal growth rate separately. Fetal growth is separated from length of gestation by either controlling for length of gestation when using birth weight as a predictor or by using weight for gestational age z-scores. The effect of length of gestation has largely been investigated via comparison of menarcheal ages of pre-term and full-term girls. An Indian study by Bhargava and colleagues (1995) found that girls born preterm reached menarche 6 months before controls and girls who suffered fetal growth retardation reached menarche 12 months earlier than controls. Lazar et al (2003) found that girls born small for gestational age (SGA) had earlier age at menarche than idiopathic short children born appropriate for gestational age (AGA). A cross-sectional study of 1060 Polish girls found a significant relationship between being SGA or AGA (by the criterion of being above or below the tenth centile for weight for gestational age) and being pre or post-menarche at 14, SGA girls were more likely to be post-menarcheal at 14 (OR: 2.54, 95% CI :1.22–5.28) (Koziel and Jankowksa 2002). However, a study of 12 full-term SGA girls and 12 controls found no difference in

age at menarche (Ghirri et al 2001). Similarly , a study from Barcelona that included 37 girls born SGA and 87 girls born AGA found no association between birth weight expressed in standard deviation scores and age at menarche (Curcoy Barcenilla et al 2004).

A study of Swedish children by Persson et al (1999) found that girls born small for gestational age had earlier menarche than girls born normal for gestational age. However, when postnatal growth patterns were controlled for this effect disappeared suggesting the accelerated pattern of childhood growth in the smaller girls was responsible for the difference in menarcheal age (Persson et al 1999). This fits with the conclusion of dos Santos Silva et al (2002) that the effects of early life on menarche may be mediated through childhood growth as well as modified through changes in fatness in childhood.

Childhood Growth

As mentioned above, links between birth weight and menarche have been suggested to be mediated or modified through childhood growth (Persson et al 1999; Cooper et al 1996, dos Santos Silva 2002). Small babies often experience a period of catch-up growth in the first years of life and catch up growth has been found to consist of a greater increase in fat than lean mass (Hediger et al 1998). Fat is suspected to influence the timing of menarche directly through three methods (conversion of androgens into estrogens by aromatisation, influencing hormone production to increase levels of more potent forms of estrogen, and by reducing the binding capacity of sex hormone binding globulin (Frisch 1987)). Thus, catch up growth may influence the maturation of the HPO axis. However, the findings of Bhargava et al (2005) indicate that menarche in girls who suffer intrauterine growth retardation is still 12 months earlier despite these girls not having caught up in weight and height.

Measures of Tissue Growth

Numerous studies have found associations between early menarche and greater weight and BMI and later menarche and lower weight and BMI. A Greek study of 345 girls found positive associations for height and BMI with age at menarche (Petridou et al 1996). Koziel and Jankowksa (2002) found that, among Polish girls, an above-normal BMI increased the chances of being post-menarcheal at age 14 (OR

7.93, 95% CI: 4.67–13.48). In a Danish study of 3743 women, those individuals who had been underweight were more like to experience menarche later (OR 3.1 (1.4-6.9)), and those with excess weight were more likely to experience early menarche (OR 5.0 (2.4-10.6)) (Helm et al 1995). A study of Brazilian girls between 10 and 18 years old found associations between overweight ($p<0.001$) and obesity ($p<0.001$) and the presence of menarche as well as associations between undernutrition ($p<0.001$) and eutrophy ($p<0.001$) with the absence of menarche (Vitalle et al 2003).

A study of Bengali Indian girls shows that within the same socioeconomic group girls with early menarche were heavier and taller than the late menarche girls (Bharati and Bharati 1998). A study of 438 girls living about 200 km away in Bangladesh found that girls who had reached menarche were less likely to be below the 5th centile for BMI in the WHO reference (OR -0.07, 95%CI 0.05-0.12) than non-menstruating girls (Chowdhury et al 2000). Menstruating girls had significantly greater weights and BMIs at ages 11, 13, 14, and 15 years and greater heights at 11 and 14 years compared to girls who had not reached menarche (Chowdhury et al 2000). Hesketh, Ding, and Tomkins (2002) found very similar results among Chinese girls among whom BMI predicted menarche and the authors note that, as the Chinese girls weighed more and were taller, pre- and post-menarche BMIs in this study were "remarkably similar" to those reported by Chowdhury et al (p. 350). Providing further verification that greater weight precedes menarche in the order of events, results from the longitudinal MRC NSHD study show that menarche occurred earlier in girls who were heavier at age 7, girls in the highest quintile of weight at age 7 achieved menarche 7.3 months earlier than the lower four quintiles (Cooper et al 1996). Though these studies represent a convincing body of evidence in support of a correlation between measures of tissue growth and menarche the significance of such a correlation is not clear and may not be causal or even permissive (Parent et al 2003) especially considering that the correlation may be due to common genetic factors as indicated by the aforementioned genetic studies (Kaprio et al 1995) or, as Ellison (2001) has pointed out, increases in fatness measured by skinfolds, BMI, and weight found to be associated with menarche may be a consequence of rising levels of estrogen due to maturation of the HPO axis rather than the cause of them. Indeed considering the finding in a longitudinal

American study of maturation of the HPO axis independent of body composition, causation may be quite unlikely (Legro et al 2000).

Measures of Skeletal Growth

As mentioned above, studies have also linked height and the timing of menarche. Several studies have linked stunting (low height for age compared to reference values) in early childhood with later menarche. A Guatemalan study found that girls categorized as severely stunted (below - 3.0 SD of the National Center for Health Statistics {NCHS} reference) at age 3 had later ages at menarche than girls who had been moderately stunted (between -3.0 and -2.0 SD of the NCHS reference) at age 3 (Khan et al 1996). Similarly girls who had not been stunted (above - 2.0 SD of the NCHS reference) at age 3 had earlier menarche than those who had been moderately or severely stunted at age 3(Khan et al 1996). This effect remained significant when SES, dietary intake, and childhood illness were held controlled for (Khan et al 1996).

A longitudinal study of rural Senegalese girls that grouped participants into three categories by height for age assessed when participants were between the ages of 2 and 5 years (< -2.0 SD, -2.0 to -1.0 SD, and > -1.0 SD of the NCHS reference) found a significant difference in ages at menarche between these groups ($p< 0.001$) (Simondon et al 1998). Ages at menarche for the groups were 17.2 yrs (95% CI: 16.6, 18.7), 16.5 yrs (95% CI 16.1,17.2) and 15.6 yrs (95% CI 15.2, 16.0 respectively (Simondon et al 1998). These same data were analysed such that girls were grouped as stunted in infancy and non-stunted, the authors found no difference in age at menarche (Benefice et al 2001). This analysis also found that the previously stunted girls caught up with the non stunted girls in stature, sitting height, and bi-acromial and biiliac width in the final year of clinical and growth assessments when they were a mean age of 15.5 years of age (Benefice et al 2001). As their finding was that there was no significant difference in age at menarche between the two groups, it seems that this catch up growth in height resulted in the lack of disparity in age at menarche. It also fits with a hypothesis that menarche is timed to coincide with attainment of a minimum size of the pelvic inlet which itself is linked to levels of sex hormones and overall skeletal growth (Ellison 1990).

Benefice et al (2001) also found that the Senegalese girls stunted in infancy accumulated more subcutaneous fat on the upper part of the body (trunk or arms) but not more total fat. This too may explain to some degree how the stunted girls were able to catch up with their non-stunted peers in sexual maturation as central accumulation of body fat has an especially strong influence on estradiol levels in adolescent girls (de Ridder et al 1990) and a Dutch study has shown an association between early menarche and truncal fat distribution in adolescence and in adulthood (van Lenthe et al 1996).

Stunting or shortness in adolescence is also associated with delayed age at menarche as shown by Leenstra and colleagues' (2005) Kenyan study that showed that being below -2.0 SD in height for age (NCHS reference) reduced the odds of being post-menarcheal (OR: 0.09, 95% CI: 0.03, 0.25). In this study, stunting reduced the odds of being post-menarcheal more than thinness (BMI for age below the 5th centile) (OR: 0.15; 95% CI: 0.07, 0.30). The Dunedin Multidisciplinary Health and Development Study of New Zealand found that height at age 7 was the most important determinant of age at menarche among weight, height and BMI measured repeatedly in childhood (St. George, Williams, and Silva 1994). Girls with early menarche had been taller at 7 but were overtaken in height by later maturers by age 15 (St. George, Williams, and Silva 1994). The authors also found that daughters of tall mothers matured later while daughters of short mothers matured earlier and were then overtaken by the daughters of tall mothers (St. George, Williams, and Silva 1994). This finding provides some indication of the influence of a genetic component on menarche, though several large studies have found that timing of menarche has no association with final height.

As mentioned above, Ellison's (1981a) reanalysis of Berkeley Guidance Study data found a reduction in variance in height as menarche was approached and another publication from the same year (1981b) of results from these data shows a series of strong multiple regression associations predicting whether participants have reached menarche by yearly height increments in the preceding year between age 9 and 13. In the strongest relationships the R^2 is 0.54 which it is for age 11 (reflecting the effect of the increment between 10 and 11) and age 12.5 (reflecting the effect of the increment between 11.5 and 12.5) (Ellison 1981b). The R^2 increases from 0.19 at

age 9 to 0.54 at age 11, after which it drops slightly to 0.51 and 0.45 for ages 11.5 and 12 respectively, after which it rises to 0.54 for age 12.5 and then drops to 0.44 for age 13 (Ellison 1981b). Ellison (1981b) uses the same regression equations on data from the Stuart growth study and reports the same level of success with height increments as a predictor. Ellison (1981b) points out that the R^2 values for these regressions are higher (except for at age 9) than those reported by Frisch in 1974 in which Frisch suggests that her regression equations should be used by doctors to predict menarche in patients. A French study following Ellison's lead found a weaker but still significant relationship between growth velocity and menarche (Elizondo 1992). Yoneyama, Nagata, and Sakamoto (1988) found that while menarche was predicted by increments of height preceding menarche, final height was not significantly different among four ordinal groups by timing of menarche (10-11.9 yrs, 12-12.9 yrs, 13-13.9 yrs, and 14-15.9 yrs) although the rate of later growth is negatively affected by age at menarche. Other studies of growth in height and age at menarche showed similar results (Tanner, Whitehouse, and Takaishi 1966; Frisch and Revelle 1969; Tsuzaki et al 1989).

However, several studies have found an association between greater adult height and later menarche (De Stavola et al 2004; Johansson and Ritzen 2005; Sharma, Talwar, and Sharma 1988) thus intrauterine growth retardation may lead to reduced final height in women through early menarche (Ibanez et al 2000). The association between greater adult height and later menarche is accounted for by the fact that increased estrogen production associated with the maturation of the HPO axis causes the growth plates in the long bones to fuse (Grumbach 2000; Eriksen et al 1988) which occurs earlier or later depending on the tempo of maturation. Findings by Zacharias and Rand (1983) that menarche is associated with spurt timing but not with growth in height during the spurt indicate a different kind of relationship between height and menarche than a simple threshold.

While the effects of stunting on menarche may be due to direct nutritional effects on maturation, maturation may be constrained by the requirement of sufficient skeletal growth for reproductive success and adequate nutrition fuels this growth. The hypothesis mentioned above that menarche may be constrained by growth and reshaping of the pelvis is evolutionary plausible in this sense because the size and

shape of the pelvis are important to successful reproduction. The female pelvis is reshaped in adolescence by the same hormones that limit long bone growth (Moerman 1982; Ellison 1982; La Velle 1995). La Velle (1995) has asserted that the pattern of variation seen in pelvic growth and reshaping indicates strong selection on the human pelvis. The hypothesis of an association between biiliac width and menarche is further supported by an analysis of data from two populations by Worthman (1993). Worthman (1993) finds that in Kikuyu (an ethnic group from Kenya) and Bundi (an ethnic group from Papua New Guinea) girls' menarche is well predicted by the time of achievement of a biiliac width of 24 cm.

Some studies have looked into relationships between menarcheal age and other indicators of skeletal growth and maturation (Marshall and Limongi 1976; Gillet-Netting, Meloy and Campbell 2004). Gillet-Netting, Meloy and Campbell (2004) found that dental maturation (based on emergence of the 2nd and 3rd molars) was a significant predictor of menarcheal status. Marshall and Limongi (1976) found a statistically significant association between menarcheal age and bone age based on radiographs of the hand and wrist in 352 British girls though this was not an improvement over the predictive power of chronological age alone. The aforementioned study by Khan et al (1996) looked at skeletal growth through the number of ossification centers of the left hand and wrist at age 3 determined by radiography and found no significant association with age at menarche and this variable was not included in multiple regression models in favour of inclusion of height for age at age 3 which was significantly associated with menarche and with which number of ossification centers was highly correlated.

C. Early Life Experience as a Determinant of Age at Menarche

Socioeconomic Differences

Studies comparing age at menarche for girls from the same region who are from different socioeconomic backgrounds have often found differences in age at menarche.

A study of Iranian girls found that socioeconomic status (SES), as calculated through an equation including father's education, mother's education, current social class according to occupation and previous social class according to occupation, was

negatively correlated with age at menarche (Ayatollahi, Dowlatabadi, and Ayatollahi 2002). A Colombian study also found SES (in 6 categories including bourgeois and proletarian) to be a strong predictor of age at menarche, the association was negative; girls from the highest socio-economic group experienced menarche 0.72 years before the poorest girls (Chavarro et al 2004). One Polish study found that age at menarche among 19,000 schoolgirls had an inverse relationship with father's educational level (Bielicki et al 1986). This same study found that when families below a certain level of social class by occupation were left out of the analysis the relationship reversed so that the lower social class group reached menarche earlier than the high social class group (Bielicki et al 1986). However, another study of 1060 Polish schoolgirls found no association between menarche and several indicators of SES (Koziel and Jankowksa 2002). In a Turkish study, no significant difference in menarcheal age between socioeconomic groups was found (Ersoy et al 2004). Petridou et al (1996) asserted that as a result of a reduction in nutritional differences between socioeconomic groups the association between age at menarche and social class in Greece has disappeared over time. The longitudinal National Child Development Study in the UK found that social class in childhood had no association with age at menarche and the authors felt that this supported a hypothesis that the timing of menarche is chiefly regulated by genetic factors and nutrition is less important in well nourished populations (Stark et al 1989).

Activity Levels

High activity levels are implicated in delayed menarche. A prospective study from Germany found that increased sports activity was associated with a delay in menarche (RR = 0.3; 95% CI 0.1-0.5; lowest vs. highest quartile) (Merzenich, Boeing, and Wahrendorf 1993). A Japanese study comparing 143 athletes and 73 non-athletes found that the time between the age at maximum peak velocity on a BMI growth curve (which did not differ between the two groups) and menarche was significantly longer for athletes (0.74±1.30 yrs for athletes vs. 0.15±0.81 yrs for controls). A retrospective Colombian study found that age at menarche was positively associated with performance of 2 or more hours of physical activity per day in adolescence (Chavarro et al 2004). A cross-sectional study of Greek girls found that even moderate physical activity was associated with a delay in menarche (Petridou et al 1996). A large scale Chinese study (n=12,727) found that menarche

was later in women who reported having done heavy physical labour compared with girls who reported having done "not heavy physical labour" (Graham et al 1999). However, physical labour is not always associated with delayed menarche. In situations where there is a clear economic benefit to offset physical labour menarche may come earlier, as has been shown in a comparison of Senegalese girls who work as migrant labourers and those who do not (Garnier et al 2003). In infancy and at the start of puberty girls who later became migrant labourers and those who did not were not different in nutritional status; however, the girls who worked as migrant labourers significantly improved their living conditions over the non-migrant girls and were more likely to have reached menarche by the 1999 data collection period when they were a mean age of 15.5 (Garnier et al 2003).

Urbanization

The aforementioned retrospective Colombian study found an independent significant negative association of age at menarche with degree of urbanization (large city, intermediate city, and small city/rural) in multivariate regression model that adjusted for family size, socioeconomic status, and level of physical activity (Chavarro et al 2004). A study of Mozambican girls that used both a retrospective method and probit analysis found a similar result, menarche was earlier in urban girls, 1.16 years earlier in the retrospective group and 0.72 years earlier in the group as assessed by probit analysis. Cameroonian and Ghanaian studies comparing menarcheal age in urban, suburban, and rural girls found very similar results (Pasquet et al 1999; Adadevoh et al 1989). A Chinese study revealed that even after adjustment for BMI, family income, age, and whether the girl was an only child, urban girls still experienced earlier menarche (Hesketh, Ding, and Tomkins 2002). In the Filipino CLHNS study, girls from urban, high socioeconomic households were found to be younger at menarche than other girls but the authors indicate the belief that this association is due to higher socioeconomic status (Adair et al 2001).

Family Effects

Associations between family size and age at menarche (Chavarro et al 2004; Billewicz, Fellowes, and Thompson 1981; Roberts, Wood and Chinn 1986; Roberts Danskin and Chinn 1975; Roberts, Rozner and Swan 1971) and birth order and age at menarche (Padez 2003; Roberts, Wood and Chinn 1986; Malina et al 1979, Malina et

al 1997) have been found in several studies. The Colombian study mentioned above found a significant positive association between menarche and family size independent of urbanization, socioeconomic status, and level of physical activity in a multiple regression model (Chavarro et al 2004). Some of the difference in age at menarche between female siblings could be due to birth order/position in family as found in the study of Mozambican girls mentioned above which found that girls born later in a family had a later age at menarche (Padez 2003). However, independent and opposing effects of birth order and family size on menarche were found in a study of girls in Cumbria; large family size was found to delay menarche, whereas later position in family was associated with early menarche (Roberts, Wood and Chinn 1986).

In a study of university athletes, Malina and colleagues (1997) found that large family size delayed menarche and found that for the total sample this effect was not changed when birth order was controlled for however the effect became stronger on the white subgroup when this was done. A large cross-sectional British study also found variation between population sub-groups in the associations between family size and birth order with menarcheal age (Ulijaszek, Evans, and Miller 1991). Ulijaszek, Evans, and Miller (1991) found that family size was positively associated with menarcheal age among European and Indo-Pakistani girls but not among Afro-Caribbean girls.

Stress

It is quite possible that some the associations of menarche with social factors, SES, urbanization, family size, etc reflect differences in nutrition/energy balance rather than independent effects, however, there is also the possibility that these affect the glucocorticoid levels and/or the hypothalamic pituitary adrenal axis (HPA) through exposure to stress which in turn affects the HPO axis. Indeed, results from some studies of children exposed to stressful life events indicate that these may delay menarche. A study of 2582 girls by Tahirović (1998) found that girls exposed to very low socioeconomic status, physical injury and psychological trauma due to war and deportation from Srebrenica to refugee camps near Tuzla had delayed menarche compared to girls living in the areas which received the refugees. Despite the acknowledged difference in nutritional conditions between the groups, Tahirović

(1998) suggests that the difference is due to the effects of stress on the hypothalamus. However, the differences in energy balance may account for the difference in age at menarche found in the study. An American study by Kim and Smith (1998) found that early attainment of menarche was associated with reported stress in family life, conflict and lack of closeness with the mother in late childhood (ages 7 to 11). In a small subsample of a larger study (n=28) by Hulanicka (2001) and colleagues found that self-reported experience of prolonged stress was associated with a menarcheal age 0.4 years later than peers. However, a California study failed to find an association between behaviour associated with greater stress (bed wetting, thumb sucking, and nightmares) and age at menarche (Campbell and Udry 1995). It seems clear that the level and duration of stress considered in these studies are unequal as, for example, injury and deportation due to war and self-reported lack of closeness with one's mother in childhood are very different stressors.

Moreover, some have interpreted the finding by numerous studies of menarche and early puberty in adoptees from the developing world in Europe as indicative of the effect of the HPA axis on maturational timing. A Swedish study of 107 adopted girls from the Indian subcontinent found that these adoptees had earlier menarche than most Indian girls and earlier menarche than Swedish girls, they also found that girls who migrated to Sweden later in childhood had earlier menarche than those who migrated earlier (Proos, Hofvander, and Tuvemo 1991). Studies that sent questionnaires to the parents of international adoptees in the United States, France and the Netherlands also found that adoptees had earlier menarche than the host population and the population of origin (Mason et al 2000; Baron et al 2000; Oostdijk et al 1996). However, the questionnaire study design used in the Dutch, French, and American studies has been criticised as concerned adoptive parents may have biased the sample (Parent et al 2003). The authors of the Swedish study (Proos, Hofvander, and Tuvemo 1991), the French study (Baron et al 2000) and the authors of a very small Belgian study (n=8) (Bourguignon et al 1992) suggest that the change from an underprivileged environment to a privileged one may be responsible for triggering early maturation via accelerated growth. A larger Belgian study by Krstevska-Konstantinova and colleagues of children (Belgian, foreign adopted, and foreign not adopted) referred to a clinic for precocious puberty found that none of the foreign children had evidence of an organic aetiology to the condition upon central

nervous system (CNS) imaging and calculated the prevalence of precocious puberty in foreign children in Belgium to be 80 times higher than for Belgian natives. The authors of this study point out that a portion of the children with precocious puberty did not show signs of having suffered from nutritional deprivation upon arrival in Belgium and point out that some of the girls in the study migrated with their with families and suggest that it is less likely that the children who migrated with their families would have suffered the kind of stress suggested to have been experienced by the adoptees, though they do not rule this out completely (Krstevska-Konstantinova et al 2001). An Italian study (Virdis et al 1998) and a Danish study (Teilmann et al 2002) also found evidence of higher rates of precocious puberty in adopted children, calculated to be 20 times higher for adoptees than other children in Denmark.

It has been suggested that intrauterine growth retardation, rather than stress, may be responsible for the early sexual development seen in adoptees in Europe (Proos et al 1992). Indeed Proos and colleagues (1992) found in their cohort of early maturing adopted girls from India in Sweden an increased likelihood of birth weight below 2.5 kg.

Nutrition

Nutrition has been directly and indirectly implicated in the timing of menarche. Correlations between BMI and menarche and weight and menarche can be interpreted as indirect implications of the effect of nutrition on the timing menarche. Some studies have also looked into the effects of specific foods or diets on menarche. Evidence for early life nutritional effects on menarche come from a study in Hawaii which found that girls who were not breastfed had earlier menarche than those who were breastfed, the authors implicate a greater deposition of fat in formula fed girls in the early maturation (Novotny et al 2003). Longitudinal data collected in the US in the early 20th century show that girls who consumed more animal protein (adjusted for overall energy in diet) at ages 3 to 5 years had earlier menarche (Berkey et al 2000). In a study of 890 girls from the United Arab Emirates univariate analysis indicated that girls who were vegetarian had later menarche, but when a multivariable analysis was performed including all variables associated with menarche in a univariate analysis, diet was not a significant predictor of age at

menarche(Badrinath et al 2004). It has been suggested that meat-eating may indicate greater fat intake and this may explain the finding of earlier menarche among meat eaters although a higher prevalence of anemia in vegetarians as a delayer of menarche has also been suggested (Badrinath et al 2004). However, an American study found no significant difference in age at menarche between vegetarian and meat eating girls (Persky et al 1992). Intake of dietary fat (adjusted for overall energy intake) was correlated with earlier menarche in a prospective study from Germany (RR: 2.1; 95% CI: 1.1-4.0; lowest vs. highest quartile) (Merzenich, Boeing, and Wahrendorf 1993). A cross-sectional Spanish study found a significant positive relationship between the inclusion of nuts and seeds in the diet of young girls and menarche (Soriguer et al 1995).

Illness in Early Life

There is some suggestion that illness in childhood may predict age at menarche. The vicious cycle of infection and malnutrition in childhood is well recognized, especially where the infection results in diarrhea (see Guerrant et al 1992; Patwari 1999, and Briend 1990 for reviews). Diarrheal infection leads to nutrient malabsorption which leads to malnutrition which predisposes to further infection. The timing of weaning is also implicated in this cycle as weaning removes the positive influence of passive immunities in breastmilk (Oddy 2002; Slade and Schwartz 1987; Goldman 1993) and breastmilk may be replaced with contaminated or nutrient poor foods which may push the child into the infection-malnutrition cycle (Long et al 1999). A Brazilian study that prospectively surveyed a village over 30 months found diarrheal incidence of more than seven episodes per child-year at six to 11 months of age among the poorest children; early weaning and poverty were risk factors for diarrhea and diarrhea led to weight loss and stunted growth (Guerrant et al 1983). Another Brazilian study with a similar design showed that the effect of the burden of diarrheal infection in the first two years of life on stunting persisted to the age of 7 (Moore et al 2001). 9.1 episodes of diarrhea before age 2, the mean, was associated with a growth shortfall of 3.6 cm (95% CI : 0.6-6.6 cm) at age 7, the end of the study period (Moore et al 2001). This effect was strong and independent of confounders such as helminthiasis, maternal education, nutritional status in infancy, and family income (Moore et al 2001). In a Bangladeshi study the cost to adult

height of each episode of prolonged diarrhea was calculated be 0.56 cm (Black, Brown, and Becker 1984).

However, a study of children up to the age of 30 months in Zimbabwe found that there was a small but not significant difference between the weight of children with frequent (more than 9 periods of diarrhea in the study period) and infrequent diarrhea (no more than 4 periods of diarrhea) (Moy et al 1994). The authors find that in the first 14 months of life these children recovered most of the weight lost (90%) in infection periods within one month and conclude that diarrhea is not a potent cause of growth faltering (Moy et al 1994). Tanner (1962) found that among British three year olds of low socioeconomic status those who had suffered four or more episodes of pneumonia or bronchitis were an average of one inch shorter than those who suffered no episodes. In one unique study that looked into the effect of early life illness on menarche, the aforementioned Guatemalan study, Khan and colleagues (1996) calculated the amount of time each participant was ill with diarrhea and ill with respiratory illnesses as percentages of the time between 3 months and 3 years of age. Neither percentage was associated with height for age scores at age 3 (Khan et al 1996). In two regression models percentage of time ill with diarrhea was a significant predictor of age at menarche (percent time ill with diarrhea: $b= -0.16 \pm 0.06$, $p< 0.01$) (Khan et al 1996).

Helicobacter pylori infection is also implicated in growth faltering (Patel et al 1994). *H. pylori* infection lasts for decades and rarely resolves itself (Parsonnet et al 1992), infection is associated with low socioeconomic status and to poor housing conditions in childhood and adulthood (Patel et al 1994; Mendall et al 1992). A Scottish study of schoolchildren from randomly selected schools in Edinburgh found that over a four year period growth in height was diminished by 1.1 cm (95% CI: 0.3 to 2.0 cm). This effect was stronger in girls whose growth was diminished 1.6 cm (95% CI: 0.4 to 2.8 cm) in the four years. A Danish study of randomly selected adults found that *H. pylori* infection detected in the study period was associated with delayed menarche (OR per year 1.10, 95% CI 1.02-1.19) (Rosenstock et al 2000).

As height is associated with age at menarche, it is conceivable that *Helicobacter pylori* or other infection may predict the timing of menarche either by affecting

growth in height or through relation to a common factor that delays both sexual maturation and growth. Another possibility is that *H. Pylori* could directly affect menarche by stimulating the immune response and thus the release of cytokines which disturb ovarian endocrine function according to Rothwell (1991) (Patel et al 1994). Beard and Blaser (2002) make strong arguments that most of the variation in human height is determined by experience of infections. One of many pieces of evidence they cite is the finding of Schmidt, Jørgensen, and Michaelsen (1995) from European data that as postneonatal mortality (which Schmidt, Jørgensen, and Michaelsen consider to be a proxy for adverse environmental factors, mainly poor nutrition and infections) drops, adult height rises. It is, however, possible that the correlations between *H. pylori* infection, diarrheal infection, respiratory infection and growth simply represent the effect of negative energy balance due to poverty/low SES.

IV. Conclusion

While it appears that there is a genetic component to timing of menarche, it is clear that developmental factors influence this timing possibly as early as during fetal life. Energetic factors such as nutrition, activity levels, and insults to the immune system, may exert a greater influence where energy balance is negative. However these and other factors may directly affect endocrine pathways and thereby influence menarche. Treolar and Martin's (1990) suggestion that menarche has the genetic appearance of a fitness trait and the correlation between menarche and pelvic maturation suggest that selection has acted on the timing of menarche. Certainly the human pelvis is considered to have been affected by competing selection for bipedalism and successful childbirth. Delayed menarche and lower ovarian steroid levels seen in many studies have been suggested to represent an adaptive response to developmental (postnatal) energetic stress that would serve to reduce fecundity to lower physiologic demands where periods of chronic nutritional stress could be expected (Ellison 1996). Effects of fetal deprivation may include reprogramming of the fetal HPO axis in accordance with a thrifty phenotype which would trigger maturation at an accelerated rate in conditions of good nutrition. This reprogramming would make sense as an adaptation on the part of the fetus expecting a situation of undernutrition. The resulting early menarche found in children born small in environments where food is not scarce may be a result of a disparity between

expectations and later circumstances. However, Kuzawa (2005) has questioned whether fetal conditions alone would have ever provided a reliable prediction of future nutritional environments and has hypothesized a non-genetic transgenerational signal of ecological conditions passed from mother to child.

V. Objectives of the Present Study

The present study uses data from the longitudinal Newcastle Thousand Families Study to test the following hypotheses:

- The timing of menarche associated with indicators of fetal conditions.
- The timing of menarche associated with measures of growth in childhood.
- The timing of menarche associated with the rates of infection suffered in the first years of life.
- The timing of menarche associated with the duration of breastfeeding.
- The timing of menarche associated with socioeconomic indicators.

The present study also tests the independence and relative strength of these associations through multi-variable analyses and attempts to control for confounders.

METHODS

Data for this study were collected between 1947 and 1997 about participants in the Newcastle Thousand Families Study. The Newcastle Thousand Families Study began in 1947 when each of the 1142 children born in May and June 1947 to mothers resident within the city of Newcastle upon Tyne was recruited into the cohort. The initial aim of the study was to investigate the causes of death in early childhood in Newcastle. However, the study was continued after the first year with yearly prospective follow-up data assessing health, growth and development collected until participants were aged 15. In smaller scale follow-ups between 1962 and 1979 the scope of investigation was further widened. Educational attainment, family background, psychosocial development, involvement in crime, and socioeconomic disadvantage were investigated. In the early 1990s, tracing study members through the National Health Service Central Register began and was followed by a publicity campaign to encourage study members to contact the study team for a large scale follow-up when the participants were 50 years of age. Through this process 832 study members were traced, comprising 89.3% of the surviving 932 children whose families stayed in Newcastle for at least the first year (Lamont et al 2000). The traced sample was found to be not statistically significantly different in social class or birth weight category (Lamont et al 1998). A postal questionnaire was sent out to contactable participants and each was invited to receive a clinical examination. 574 participants completed the questionnaire and clinical examinations were performed on 412 participants.

Collection of variables

Neonatal measures

Birth weight and gestation length were collected from domiciliary midwifery service or maternity hospital records. Birth weights were standardized for gestational age and gender in order to separate the impact of fetal growth rate from the effect of gestational age at delivery on birth weight (Leon et al 1998). Both birth weight and standardized birth weight were used in analyses to make results comparable both to studies that use birth weight alone and studies that use birth weight standardized for gestational age and gender.

Social Circumstances in Childhood

Socio-economic status during childhood was derived prospectively from the contemporary UK Registrar General's Standard Occupational Classification based on paternal occupation at birth and the occupation of the main wage-earner in the household when the children were 5 yrs old (Spence et al 1954). Social class of participants in 1947 was originally coded into 5 categories: I (Professional occupations, the most advantaged), II (Managerial and Technical occupations), III (Skilled occupations), IV (Partly-skilled occupations), and V (Unskilled occupations). As there were fewer participants in the most and least advantaged social classes, social class was regrouped (I and II, III, IV and V) to create categories of more comparable size. Social class of participants in 1952 was originally coded into 6 categories: I, II, IIIN (non-manual), IIIM (manual), IV, V. Again, as there were fewer participants in the extreme social classes, these were re-grouped as: I and II, IIIN, IIIM, IV and V. Housing conditions at birth were assessed by a housing survey carried out by the Public Health Department in the City, and scored for the presence of overcrowding, lack of hot water, toilets shared between households, and dampness or poor repair. For these analyses, those participants whose housing was found to have more than two of the problems for which the housing was scored were grouped together. Thus, the potential six categories were reduced to three categories of a more equal size, i.e. housing with none of the five problems, housing with one of the five problems, and housing with two or more of the five problems.

Breastfeeding duration

The study recruited health visitors to collect data for the study in the first years of life. Health visitors were given a specially designed book for each study participant for recording data collected during visits. The number of days that participants were breastfed was calculated from health visitor records providing the date of final breastfeeding.

Position in Family

Position in family was calculated from the number of older surviving siblings, including half siblings, at birth (Spence et al 1954). As most participants were either the first or second surviving child in their family those who were the third child or

higher up to the tenth child in the family were grouped together to make more comparable group sizes.

Illness in Childhood

Data on illnesses in childhood among the participants in the study was were collected prospectively from a variety of sources including health visitor's books, doctor's report forms, hospital notes, and telephone calls from family doctors to report illnesses. The original definition used for illness in the study is "any episode in which there was evident alteration in the infant's well-being and activity, or for which the child was taken to the family doctor or hospital"(Spence et al 1954). The illness data was used to create three variables which have been named Respiratory Infection Rate, Intestinal Infection Rate, and Overall Infection Rate. Respiratory infections represented the largest number of infections recorded. Intestinal infections, while not a large proportion of the infections recorded, represent an important variable because of the potential for effects on growth and development. Overall Infection Rate is intended to reflect the extent of general challenge to the child's immune system. 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. Those participants who temporarily left the study in childhood before age 2 were excluded from analyses. A list of the infections used to calculate the infections rates is below.

<u>Intestinal Infections Included</u>

Intestinal infection ill defined

Alimentary infection

Diarrhoea

Dysentery

Gastroenteritis Type 1 a

Gastro enteritis

Vomiting and aches and diarrhoea

Respiratory Infections Included

cute respiratory infection
Acute Upper Respiratory Infection-unspecified
Catarrh
Clear nasal discharge
Cold
Coryza, heavy breathing
Cough
Hard cough
Head cold
Infection of pharynx
Laryngitis
Loose Cough
Mild cold
Persistent profuse nasal discharge
Pharyngitis
Purulent nasal discharge
Respiratory infection
Rhinitis
Runny nose watery nasal discharge
Rattling cough
Severe cold
Sinusitis
Snuffles
Sore throat
Tickly cough
Tonsillitis
Tonsillitis and adenitis
Tonsillitis with erythema
Tonsils and adenoids problem
Upper Respiratory Infection-unspecified
Bronchiectatis
Bronchitis
Bronchitis with wheeze
Bronchopneumonia
Chest cold
Chronic bronchitis
Low-grade pneumonitis
Pneumonia
Pertussis
Whooping cough
Asian flu
Flu
Gastric flu
Influenza
Calcified primary complex (indication of Tuberculosis)
Mantoux positive/Jelly Patch + (indication of Tuberculosis)
Military tuberculosis
Oral primary tuberculosis
Pulmonary tuberculosis

Overall Infections Included

Measles
Acute otitis media
Chronic otitis media
Discharging ear
Earache
Middle ear infection
Opaque left antra
Otitis externa
Otitis/Otitis media
Ottorhoea
Chicken pox
Abscess of face
Abscess of leg
Axillary abscess
Boil on chin
Cellulitis including onychia
Ichthyosis
Impetigo
Septic cyst
Septic lesions
Boils
Crop of spots (understood to be unspecified skin infection)
Skin sepsis
Staph erythema multiforme
Staph infection (few boils)
Mumps
German measles
Rubella
Conjunctivitis
Eve discharging
Eye sore and swollen
Sticky eye
Adenitis
Both sides of neck swollen
Cervical glands swollen
Feverish
Haemolytic streptococcus
Lymph node
Lymphadenitis
Mesenteric adenitis
Pyrexia
Blepharitis
Stye
Hepatitis
Infective hepatitis
Jaundice
Yellow jaundice
Herpes
Herpetic
Herpetic stomatitis
Scarlet fever
Scarletina
Eczema
Infective eczema
Swollen glands
Sepsis
Appendix
Perforated appendix
Pyuria
Urinary infection
Dermatitis
Glandular fever
Non paralytic polio
Polio
Meningitis meningococcal

Measures of Childhood Growth

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 (Tanner, Whitehouse, and Takaishi 1966; Gairdner and Pearson 1971; Cole 1990). These variables were named standardized height at age 9 and standardized weight at age 9. Body Mass Index (BMI) at age 9 was calculated using the following formula BMI = weight at age 9 in kg/(height at age 9 in m)^2. Two variables to reflect childhood catch-up growth up to age 9 in height and weight were derived from the standardized residuals from a linear regression of standardized height at 9 on birth weight standardized for gender and gestational age and a linear regression of standardized weight at 9 on birth weight standardized for gender and gestational age, respectively. This method is similar to that suggested and used by others (Esrey, Casella, and Habicht 1990; Adair 1999; Cameron, Preece, and Cole 2005).

Menarche

Age at menarche was collected retrospectively via a postal questionnaire in the follow-up data collection when study participants were aged 50. Due to the results of analyses of recall of menarcheal age in the MRC NSHD cohort (appendix), age at menarche was used both as a continuous variable and as a categorical variable. The categorical version of age at menarche was derived by dividing participants into three groups based on whether their menarche occurred early, average, or late. The divisions were made with respect to difference from the sample mean (μ = 12.94 years). Those whose age at menarche was more than one standard deviation (SD = 1.54) less than the mean age at menarche were placed in the early menarche (<11.4 years). Those whose age at menarche was more than one standard deviation greater than the mean age at menarche were placed in the late menarche group (>14.49 years). Those whose age at menarche was less than one standard deviation greater or less than the mean age at menarche were placed in the average menarche group (11.41-14.48 yrs).

Statistical procedures

The statistical software package SPSS, version 12, was used for all statistical analyses. Descriptive statistics were calculated for all variables. All variables were inspected for normality. Several variables were not normally distributed and non-parametric tests were used with these variables where appropriate. Twins were excluded from all analyses because of effects on fetal growth; four individuals were excluded on this basis. Correlations were assessed between all continuous variables to describe association and help subsequent interpretation: Pearson correlation for pairs of normally distributed continuous variables, Spearman correlations for pairs of variables including at least one variable that was not normally distributed. Similarly, categorical and continuous variables were tested for associations using ANOVA or Kruskal Wallis tests as appropriate.

Where menarcheal age was used as a continuous variable, linear regression was used to test all other variables as predictors of age at menarche and multiple regression was used to test predictive models. Where menarcheal age was assigned to categories, ordinal logistic regression was used as it can fit models with a dependent variable with polychotomous ordered categories. As the underlying dependent variable was continuous, the probit link function was used. Ordinal logistic regression was used to test all other variables as predictors of age at menarche in univariate ordinal logistic regression and multiple ordinal logistic regression was used to test predictive models. Tests were performed to assure the assumptions of homoscedasticity, independent normally distributed errors, and lack of multicollinearity were met and to check for outliers in all significant multiple regression models. Homoscedasticity was tested via inspection of a scatterplot standardized residuals against standardized predictions of the model. A Durbin-Watson statistic was used to test for independence of errors. Normality of errors was tested via both a P-P plot and a histogram of the residuals. The assumption of lack of multicollinearity was tested by looking at the tolerance value and variance inflation factor of each significant model. For the final multi-variable ordinal logistic regression model, the assumption of proportional odds was tested. In the results section, Oprobit coefficient refers to the coefficient of the variable in the ordered logistic regression model into which it was entered. Unstandardized β coefficients, referred to as B coefficients, are reported for linear and multiple linear regression results.

Interactions between fetal conditions and childhood growth have been indicated in previous research (e.g. Cooper et al 1996, dos Santos Silva et al 2002). Thus, interactions between variables representing indicators of fetal conditions and measures of childhood growth in the multiple regression and ordinal logistic regression models were explored by entering interaction terms into regression models. Interaction terms were computed by centring the variables involved and multiplying the two dependent variables together. In models containing interaction terms other predictor variables were also centred. Multiple regression equations including the interaction term were presented to show the simple slope of the interaction at different values of one of the dependent variables. These relationships were graphed using ModGraph-I Version 1.0 (Jose 2003). Ordinal logistic regression interactions were not presented in equations or graphs because of the relative complexity of the ordinal logistic regression equation.

RESULTS

Tables 1 and 2 show descriptive statistics for all variables in the analyses.

Table 1: Descriptive statistics for continuous variables

Variable	N	Mean ± SD	Median	Range	Interquartile Range
Menarche (years)	276	12.94 ± 1.54	13.00	9	2.50
Standardized birth weight	276	0.05 ± 1.10	0.00	7.86	1.49
Unstandardized birth weight (kg)	276	3.39 ± 0.51	3.34	2.89	0.67
Gestation Length (weeks) †	276	39.80 ± 1.29	40.00	16	0.00
Weight at age 9 (kg) †	214	27.16 ± 4.67	26.70	34.90	5.43
Height at age 9 (cm)	214	128.49 ± 6.50	128.20	41.90	7.60
Standardized weight at age 9	214	-0.53 ± 0.94	-0.48	5.51	1.33
Standardized height at age 9	214	-0.77 ± 1.11	-0.75	7.04	1.34
BMI at age 9	214	16.41 ± 2.10	16.15	17.94	2.14
Duration of Breastfeeding (days) †	204	113.46 ± 116.60	59.50	443	175.75
Respiratory Infection Rate (Infections per year) †‡	274	1.16± .75	1.00	5.00	0.78
Intestinal Infection Rate (Infections per year) †‡	274	0.15 ± .19	0.11	1.00	0.22
Overall Infection Rate (Infections per year) †‡	274	1.74 ± .92	1.67	5.00	1.00
Catch Up Growth in Height	214	0.00 ± 1.00	0.01	6.23	1.23
Catch Up Growth in Weight	214	0.00 ± 1.00	0.03	5.85	1.41

† Variable is not normally distributed.
‡ 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.

Table 2: Descriptive statistics for categorical and ordinal variables

Variable	N (%)
Social Class at Birth:	n=273
1, 2	24 (8.8)
3	179 (65.6)
4, 5	70 (25.3)
Social Class at age 5:	n=276
1, 2	18 (7.5)
3N	33 (13.8)

3M	101 (42.1)
4, 5	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 the following found upon inspection: overcrowding, no hot water, shared toilet, damp, or poor repair

The results of Pearson and Spearman correlations run on all the continuous variables to examine the data for relationships between all pairs of variables are presented in Table 3. Birth weight showed a significant positive correlation with height at age 9, standardized height at age 9, gestation length and standardized birth weight. Standardized birth weight was also significantly positively correlated with height at age 9 and standardized height at age 9. Gestation length showed significant negative correlations with both intestinal infection rate and respiratory infection rate. Overall infection rate showed significant positive correlations with intestinal infection rate and respiratory infection rate. Weight at age 9 showed significant positive correlations with all the growth related variables while height at age 9 showed significant positive correlations with all growth variables except for BMI at age 9, with which it showed no significant correlation. Standardized weight at age 9 showed significant positive correlations with duration of breastfeeding and standardized height at age 9. Catch up growth in weight showed significant positive correlations with BMI at age 9, duration of breastfeeding, and catch up growth in height.

Table 3: Correlations Between Variables

		Catch Up Growth in Weight	Catch Up Growth in Height	Overall Infection Rate (birth to age 8)	Intestinal Infection Rate (birth to age 8)	Respiratory Infection Rate (birth to age 8)	Duration of Breastfeeding (days)	BMI at age 9	Standardized height at age 9	Standardized weight at age 9	Height at age 9 (cm)	Weight at age 9 (kg)	Gestation (weeks)	Birth weight (kg)	Standardized birth weight
Standardized birth weight	Corr Coeff	0.000	0.000	0.001†	-0.031†	0.031†	0.115†	-0.019	0.169*	0.081	0.173*	0.077†	-0.067†	0.809**	1
	N	214	214	274	274	274	204	214	214	214	214	214	276	276	276
Birth weight (kg)	Corr Coeff	0.061	0.084	-0.062†	-0.042†	-0.037†	0.124†	0.002	0.216**	0.125	0.215**	0.093†	0.300**	1	
	N	214	214	274	274	274	204	214	214	214	214	214	276	276	
Gestation (weeks)	Corr Coeff	0.061†	0.093†	-0.172†**	-0.061†	-0.181†**	0.038†	0.012†	0.061†	0.054†	0.052†	0.041†	1		
	N	214	214	274	274	274	204	214	214	214	214	214	276		
Weight at age 9 (kg)	Corr Coeff	0.991†**	0.678†**	0.012†	0.023†	0.050†	0.170†	0.703†**	0.677†**	0.995†**	0.669**	1			
	N	214	214	213	213	213	156	214	214	214	214	214			
Height at age 9 (cm)	Corr Coeff	0.0621**	0.981**	0.042†	-0.009†	0.096†	0.115†	0.023	0.996**	0.633**	1				
	N	214	214	213	213	213	156	214	214	214	214				
Standardized weight at age 9	Corr Coeff	0.997**	0.635**	0.003†	0.031†	0.039†	0.164†*	0.760**	0.640**	1					
	N	214	214	213	213	213	156	214	214	214					
Standardized height at age 9	Corr Coeff	0.628**	0.986**	0.040†	0.000†	0.090†	0.116†	0.024	1						
	N	214	214	213	213	213	156	214	214						
BMI at age 9	Corr Coeff	0.764**	0.028	-0.030†	0.012†	-0.027†	0.057†	1							
	N	214	214	213	213	213	156	214							
Duration of Breastfeeding (days)	Corr Coeff	0.162†*	0.083†	0.000†	-0.076†	0.034†	1								
	N	156	156	203	203	203	204								
Respiratory Infection Rate (birth to age 8)	Corr Coeff	0.043†	0.098†	0.877†**	0.100†	1									
	N	213	213	274	274	274									
Intestinal Infection Rate (birth to age 8)	Corr Coeff	0.028†	0.003†	0.331†**	1										
	N	213	213	274	274										
Overall Infection Rate (birth to age 8)	Corr Coeff	0.007†	0.048†	1											
	N	213	213	274											
Catch Up Growth in Height	Corr Coeff	0.638**	1												
	N	214	214												
Catch Up Growth in Weight	Corr Coeff	1													
	N	214													

*. Correlation is significant at the 0.05 level (2-tailed) **. Correlation is significant at the 0.01 level (2-tailed)

† Indicates Spearman Correlation results, all others are Pearson Correlation

The results of tests of association between continuous variables and categorical variables are presented in Table 4. The ANOVA revealed significant relationships between order of birth in family and standardized and unstandardized birth weight to the effect that some of the variation in both measures of birth weight is explained by the position of the participant in her family. Both standardized and unstandardized birth weight in this group increased as the number of surviving older siblings increased. The ANOVA and Kruskal-Wallis results for associations between order of birth in family with each of weight at age 9, height at age 9, standardized weight at age 9, height for age z-score at 9, catch up growth in height, and catch up growth in weight each show the same pattern of decrease for each increase in number of surviving older siblings. Birth weight and gestation also show significant relationships with the housing conditions assessed when participants were age 5 although these finding cannot be considered meaningful because of the temporal nature of the data.

Table 4 : Associations between Categorical and Continuous Variables

		Social Class in 1947 (3 Groups: I &II, III, IV&V)	Social Class in 1952 (4 Groups: I &II, IIIN, IIIM, IV&V)	Housing Conditions at Birth (0, 1, ≥2)†	Housing Conditions at Age 5 (0, 1, ≥2)†	Order of Birth in Family (1st, 2nd, 3rd or higher)‡
Standardized birth weight	ANOVA Sig. (2-tailed)	0.955	0.832	0.954	0.502	0.002**
	N	273	240	276	249	276
Birth weight (kg)	ANOVA Sig. (2-tailed)	0.917	0.666	0.521	0.036*	0.000**
	N	273	240	276	249	276
Gestation (weeks)	Kruskal-Wallis Asymp. Sig.	0.129	0.955	0.678	0.050*	0.101
	N	273	240	276	249	276
Weight at age 9 (kg)	Kruskal-Wallis Asymp. Sig.	0.143	0.323	0.424	0.923	0.024*
	N	212	204	214	213	214
Height at age 9 (cm)	ANOVA Sig. (2-tailed)	0.204	0.125	0.198	0.714	0.003**
	N	212	204	214	213	214
Standardized weight at age 9	ANOVA Sig. (2-tailed)	0.103	0.290	0.442	0.898	0.023*
	N	212	204	214	213	214
Standardized height at age 9	ANOVA Sig. (2-tailed)	0.220	0.138	0.203	0.721	0.003**
	N	212	204	214	213	214
BMI at age 9	ANOVA Sig. (2-tailed)	0.380	0.702	0.561	0.668	0.191
	N	212	204	214	213	214
Duration of Breastfeeding (days)	Kruskal-Wallis Asymp. Sig.	0.239	0.948	0.464	0.820	0.760
	N	202	178	204	183	204
Respiratory Infection Rate§ (birth to age 8)	Kruskal-Wallis Asymp. Sig.	0.151	0.652	0.787	0.975	0.159
	N	271	240	274	249	274
Intestinal Infection Rate§ (birth to age 8)	Kruskal-Wallis Asymp. Sig.	0.870	0.557	0.074	0.200	0.329
	N	271	240	274	249	274
Overall Infection Rate§ (birth to age 8)	Kruskal-Wallis Asymp. Sig.	0.213	0.760	0.722	0.382	0.079
	N	271	240	274	249	274
Catch Up Growth in Height	ANOVA Sig. (2-tailed)	0.208	0.156	0.174	0.634	0.001**
	N	212	204	214	213	214
Catch Up Growth in Weight	ANOVA Sig. (2-tailed)	0.100	0.276	0.419	0.914	0.011*
	N	212	204	214	213	214

† Number of the following found upon inspection: overcrowding, no hot water, shared toilet, damp, or poor repair ‡ Counting surviving children only

§ 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.

* Correlation is significant at the 0.05 level (2-tailed)

** Correlation is significant at the 0.01 level (2-tailed

The results of univariate ordinal logistic regression of age at menarche on continuous variables are presented in Table 5. Results of ordinal logistic regression analyses should be interpreted in keeping with the fact that 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. Neither standardized nor unstandardized birth weight were found to be significant predictors of menarcheal age group and length of gestation approached significance. The continuous variables representing measures of tissue growth in childhood were all found to be significant predictors of menarcheal age group at the 0.001 level and each has a negative coefficient. These were weight at age 9, standardized weight at age 9, BMI at age 9, and catch up growth in weight. The ordinal logistic regression coefficient of standardized weight at age 9 was the largest of all significant predictors while weight at age 9 had a relatively small coefficient. None of the variables representing skeletal growth in childhood were found to be significant predictors. The duration of breastfeeding and the childhood illness rates were also not significant predictors of menarcheal age group.

Table 5: Predictors by Menarcheal Age Category - Mean ± Standard Deviation and Ordinal Logistic Regression Results

Variable	N	Early (<11.4 years)	Average (11.41-14.48)	Late (>14.49 years)	Oprobit Coefficient	95% CI	p value
Standardized birth weight	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
Weight at age 9 (kg)	214	28.77 ± 6.18	27.20 ± 4.23	25.12 ± 2.86	-0.066	-0.10, -0.03	<0.001
Height at age 9 (cm)	214	129.56 ± 6.31	128.45 ± 6.43	127.31 ± 6.88	-0.019	-0.04, 0.00	0.105
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
Duration of Breastfeeding (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)‡	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)‡	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)‡	274	1.93 ± 1.01	1.64 ± 0.86	1.87 ± 0.95	-0.040	-0.19, 0.11	0.590
Catch Up Growth in Height	214	0.14 ± 0.97	-0.00 ± 0.99	-0.17 ± 1.06	-0.115	-0.27, 0.04	0.141
Catch Up Growth in Weight	214	0.30 ± 1.10	0.02 ± 0.98	-0.43 ± 0.78	-0.276	-0.43, -0.12	0.001

‡ 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.

The results of regression of continuous age at menarche on continuous predictors are presented in Table 6. These results are similar to those of Table 5, however, birth weight approached significance as a predictor of menarche and gestation length was a significant positive predictor of age at menarche at the 0.05 level.

Table 6: Linear Regression Results for Continuous Variables as Predictors of Timing of

Variable	N	B coefficient	95% CI	p value
Birth weight standardized for gestational age	276	0.054	-0.11, 0.22	0.527
Birth weight (kg)	276	0.335	-0.02, 0.69	0.064
Gestation Length (weeks)	276	0.159	0.02, 0.30	0.027
Weight at age 9 (kg)	214	-0.082	-0.13, -0.04	<0.001
Height at age 9 (cm)	214	-0.020	-0.05, 0.01	0.217
Standardized weight at age 9	214	-0.393	-0.61, -0.18	<0.001
Standardized height at age 9	214	-0.110	-0.30, 0.08	0.247
BMI at 9	214	-0.177	-0.27, -0.08	<0.001
Duration of Breastfeeding (days)	204	<0.001	-0.00, 0.00	0.993
Respiratory Infection Rate (Infections per year)‡	274	0.033	-0.21, 0.28	0.792
Intestinal Infection Rate (Infections per year)‡	274	-0.139	-1.09, 0.81	0.733
Overall Infection Rate (Infections per year)‡	274	-0.057	-0.26, 0.14	0.571
Catch Up Growth in Height	214	-0.127	-0.17, 0.25	0.227
Catch Up Growth in Weight	214	-0.372	-0.57, -0.17	<0.001

Menarche

‡ 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.

The results of testing categorical variables as predictors of menarcheal age group using ordinal logistic regression are presented in Table 7. None of these models achieve statistical significance.

Table 7: Ordinal Logistic Regression Results for Categorical Variables as Predictors of Timing of Menarche

Variable	Categories	N	Mean ± SD	Oprobit Coefficient	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
	IIIN	33	13.34 ± 1.56	0.097	-0.36, 0.55	0.675
	IIIM	101	13.09 ± 1.50	-0.013	-0.34, 0.31	0.938
	IV & V	88	12.88 ± 1.54	-	-	0.968
	Model	240	13.03 ± 1.50	0.042	-	0.887
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 the following found upon inspection: overcrowding, no hot water, shared toilet, damp, or poor repair

The results of regression of menarche on categorical variables did not reveal any significant categorical predictors of age at menarche (Table 8).

Table 8: Linear Regression Results for Categorical Variables

Variable	Categories	B coefficient	95% CI	p value
Social Class in 1947	I & II	0.548	-0.17, 1.27	0.134
	III	0.402	-0.03, 0.83	0.065
	IV & V	-	-	-
	Model	-	-	0.134
Social Class in 1952	I & II	-0.051	-0.82, 0.71	0.896
	IIIN	0.454	-0.15, 1.06	0.139
	IIIM	0.208	-0.22, 0.64	0.343
	IV & V	-	-	-
	Model	-	-	0.441
Housing Conditions at Birth*	0	0.158	-0.29, 0.60	0.484
	1	0.092	-0.40, 0.59	0.715
	≥2	-	-	-
	Model	-	-	0.782
Housing Conditions at Age 5*	0	0.465	-0.03, 0.96	0.065
	1	0.469	-0.08, 1.02	0.094
	≥2	-	-	-
	Model	-	-	0.149
Order of Birth in Family	1st	-0.461	-0.91, -0.01	0.045
	2nd	-0.220	-0.73, 0.29	0.394
	3rd or higher	-	-	-
	Model	-	-	0.122

*Number of the following found upon inspection: overcrowding, no hot water, shared toilet, damp, or poor repair

In order to look for relationships with menarcheal age that may have been obscured by the relationship between menarche and standardized weight at age 9 (the strongest predictor of menarche in univariate analyses), as well as to test for effects these variables may have on the predictive power of standardized weight at age 9, multi-variable models including standardized weight at age 9 and one other predictor have

been tested. Multi-variable ordinal logistic regression models each including standardized weight at age 9, and another continuous variable were tested for their prediction of menarcheal age group (Table 9). Controlling for birth weight, standardized birth weight, length of gestation, duration of breastfeeding, height at age 9, standardized height at age 9, catch up growth in height each caused a small to moderate increase in the absolute value of the ordinal logistic regression coefficient of standardized weight at age 9 and high significance was maintained. However, controlling for standardized weight at age 9 had little effect on any of the other continuous variables. Controlling for BMI or catch up growth in weight in an ordinal logistic regression model caused standardized weight at age 9 to lose significance in predicting menarcheal age group. However, as BMI and weight are both measures of tissue growth in childhood, one would expect controlling for one to considerably reduce the significance of the other.

Table 9: Ordinal Logistic Regression Results for Models including standardized weight at age 9 and Continuous Variables

Variable	Oprobit coefficient (Controlling for standardized weight)	95% CI	p value	Oprobit coefficient of standardized weight when variable (left) is controlled	95% CI	p value
Birth weight standardized for gestational age	-0.006	-0.15, 0.13	0.934	-0.295	-0.46, -0.13	0.001
Birth weight (kg)	0.152	-0.15, 0.45	0.320	-0.306	-0.48, -0.14	<0.001
Gestation Length (weeks)	0.119	-0.00, 0.24	0.057	-0.311	-0.48, -0.14	<0.001
Height at age 9 (cm)	0.011	-0.02, 0.04	0.462	-0.346	-0.56, -0.13	0.002
Standardized height at age 9	0.085	-0.10, 0.27	0.353	-0.361	-0.58, -0.14	0.001
BMI at 9	-0.063	-0.18, 0.05	0.279	-0.192	-0.44, 0.06	0.135
Duration of Breastfeeding (days)	0.000	-0.00, 0.00	0.566	-0.332	-0.53, -0.14	0.001
Respiratory Infection Rate (Infections per year)‡	0.047	-0.24, 0.33	0.747	-0.293	-0.46, -0.13	0.001
Intestinal Infection Rate (Infections per year)‡	0.210	-0.75, 1.17	0.666	-0.293	-0.46, -0.13	0.001
Overall Infection Rate (Infections per year)‡	0.001	-0.22, 0.23	0.994	-0.292	-0.46, -0.13	0.001
Catch Up Growth in Height	0.097	-0.10, 0.30	0.340	-0.362	-0.58, -0.15	0.001
Catch Up Growth in Weight	0.080	-1.81, 1.97	0.934	-0.380	-2.39, 1.63	0.710

Multiple regression models each including standardized weight at age 9, and another continuous variable were tested for their prediction of menarcheal age (Table 10). Adjusting for standardized weight at age 9 made no improvement on the significance of the infection rate variables as predictors of menarcheal age. When BMI at age 9 or catch up growth in weight were controlled, standardized weight at age 9 lost significance. Controlling for each of the three infections rate variables caused a small decrease in the weight of the B coefficient of standardized weight at age 9. Controlling for all other continuous variables caused small to moderate increases in the B coefficient of standardized weight at age 9 and maintenance of high

significance. Adjusting for standardized weight at age 9 increased the weight of the B coefficient of birth weight and caused a change in p value from 0.064 to 0.041. Similarly, adjusting for standardized weight at age 9 increased the weight of the B coefficient of gestation as a predictor of age at menarche and caused it to become highly significant. Adjusting for standardized weight at age 9 had little effect on duration of breastfeeding, catch up growth in height, height at age 9 and standardized height at age 9 as predictors of age at menarche as all maintain non-significance.

Table 10: Multiple Regression Results for Models including standardized weight at age 9 and Continuous Variables

Variable	B coefficient (Controlling for standardized weight)	95% CI	p value	B coefficient of standardized weight when variable (left) is controlled	95% CI	p value
Birth weight standardized for gestational age	0.046	-0.14, 0.23	0.620	-0.397	-0.61, -0.18	<0.001
Birth weight (kg)	0.406	0.02, 0.80	0.041	-0.421	-0.64, -0.21	<0.001
Gestation Length (weeks)	0.203	0.05, 0.35	0.008	-0.416	-0.63, -0.20	<0.001
Height at age 9 (cm)	0.026	-0.01, 0.07	0.193	-0.508	-0.79, -0.23	<0.001
Standardized height at age 9	0.174	-0.06, 0.41	0.147	-0.524	-0.80, -0.25	<0.001
BMI at 9	-0.104	-0.25, 0.04	0.162	-0.215	-0.54, 0.11	0.200
Duration of Breastfeeding (days)	0.001	-0.00, 0.00	0.544	-0.464	-0.71, -0.21	<0.001
Respiratory Infection Rate (Infections per year)‡	0.098	-0.27, 0.47	0.604	-0.388	-0.60, -0.17	<0.001
Intestinal Infection Rate (Infections per year)‡	0.141	-1.11, 1.39	0.825	-0.386	-0.60, -0.17	<0.001
Overall Infection Rate (Infections per year)‡	0.043	-0.25, 0.34	0.774	-0.387	-0.60, -0.17	<0.001
Catch Up Growth in Height	0.180	-0.08, 0.44	0.175	-0.514	-0.79, -0.24	<0.001
Catch Up Growth in Weight	-0.628	-3.12, 1.86	0.620	0.273	-2.38, 2.93	0.839

Ordinal logistic regression models including standardized weight at age 9 and each of 5 categorical variables as predictors of menarcheal age group were tested (see Table 11). Controlling for standardized weight at age 9 had little effect on the categorical variables in ordinal logistic regression models and none achieved significance.

Table 11: Ordinal Logistic Regression Results for Models including standardized weight at age 9 and Categorical Variables

Variable	Categories	Oprobit coefficient (Controlling for standardized weight)	95% CI	p value	Oprobit coefficient of standardized weight when variable (left) is controlled	95% CI	p value
Social Class in 1947	I & II	0.172	-0.59, 0.94	0.660	-0.307	-0.48, -0.14	<0.001
	III	0.180	-0.18, 0.54	0.325			
	IV & V	-	-	-			
	Model	-	-	-	-	-	0.004
Social Class in 1952	I & II	0.064	-0.63, 0.76	0.856	-0.311	-0.49, -0.14	<0.001
	IIIN	-0.032	-0.55, 0.49	0.905			
	IIIM	-0.038	-0.39, 0.31	0.831			
	IV & V	-	-	-			
	Model	-	-	-	-	-	0.012
Housing Conditions at Birth	0	-0.112	-0.49, 0.27	0.559	-0.299	-0.47, -0.13	<0.001
	1	-0.036	-0.37, 0.44	0.863			
	≥2	-	-	-			
	Model	-	-	-	-	-	0.005
Housing Conditions at Age 5	0	0.076	-0.33, 0.48	0.714	-0.294	-0.46, -0.13	0.001
	1	0.155	-0.29, 0.60	0.498			
	≥2	-	-	-			
	Model	-	-	-	-	-	0.006
Order of Birth in Family	1st	-0.211	-0.59, 0.17	0.277	-0.280	-0.45, -0.11	0.001
	2nd	-0.215	-0.63, 0.20	0.314			
	3rd or higher	-	-	-			
	Model	-	-	-	-	-	0.003

Multiple regression models including standardized weight at age 9 and each of 5 categorical variables as predictors of age at menarche were tested (see Table 12). Results are very similar to those in Table 11 in that no categorical predictors achieved significance when standardized weight at age 9 is controlled. Likewise, controlling for categorical predictors had little effect on standardized weight as a predictor of menarche.

Table 12: Multiple Regression Results for Models including standardized weight at age 9 and Categorical Variables

Variable	Categories	B coefficient (Controlling for standardized weight)	95% CI	p value	B coefficient of standardized weight when variable (left) is controlled	95% CI	p value
Social Class in 1947	I & II	0.639	-0.37, 1.65	0.214	-0.420	-0.64, -0.20	<0.001
	III	0.401	-0.07, 0.87	0.095			
	IV & V	-	-	-			
	Model	-	-	-	-	-	0.001
Social Class in 1952	I & II	0.045	-0.86, 0.95	0.921	-0.411	-0.63, -0.19	<0.001
	IIIN	0.450	-0.22, 1.12	0.189			
	IIIM	0.190	-0.26, 0.64	0.407			
	IV & V	-	-	-			
	Model	-	-	-	-	-	0.006
Housing Conditions at Birth	0	0.051	-0.45, 0.55	0.842	-0.395	-0.61, -0.18	<0.001
	1	0.079	-0.46, 0.62	0.773			
	≥2	-	-	-			
	Model	-	-	-	-	-	0.005
Housing Conditions at Age 5	0	0.390	-0.14, 0.92	0.147	-0.392	-0.60, -0.18	<0.001
	1	0.489	-0.09, 1.07	0.100			
	≥2	-	-	-			
	Model	-	-	-	-	-	0.002
Order of Birth in Family	1st	-0.257	-0.76, 0.24	0.313	-0.371	-0.59, -0.15	0.001
	2nd	-0.110	-0.66, 0.44	0.695			
	3rd or higher	-	-	-			
	Model	-	-	-	-	-	0.003

Assumptions were not violated in any statistically significant model. Participants whose gestation was shorter than 37 weeks were removed from the sample and the multiple regression re-run to determine whether the exclusion of pre-term births would affect the relationship between length of gestation and age at menarche, however, as removing these strengthened the relationship, the effect is not simply

caused by premature births of some participants in the study. Thus these participants' data were re-included.

Models containing interaction terms were run using ordinal logistic regression and multiple regression to look for interactions between standardized weight at age 9 and other variables related to fetal conditions including birth weight, standardized birth weight and gestation length. A significant interaction was found between standardized weight at age 9 and standardized birth weight in both ordinal logistic regression (p=0.030) and multiple regression models (p=0.043).

The multiple regression equation for the model containing the interaction term is

age at menarche=12.991– 0.380 * WAZ at 9 + 0.028 * sds bw – 0.233 * WAZ at 9* sds bw

(where WAZ is standardized weight at age 9 and sds bw is standardized birth weight)

which can be rearranged to

age at menarche= (–0.380 – 0.233 * sds bw) * WAZ at 9 + 12.991 + 0.028* sds bw,

making the area in parentheses the simple slope of the equation.

The regression equation for high standardized birth weight (+1 SD) is

age at menarche= (-0.636279)* WAZ at 9 + 12.991 + 0.028* sds bw

t= -0.47, p=0.64,

for average standardized birth weight (z-score = 0) is

age at menarche=(-0.38)* WAZ at 9 + 12.991 + 0.028* sds bw, and

t= -0.40, p=0.69,

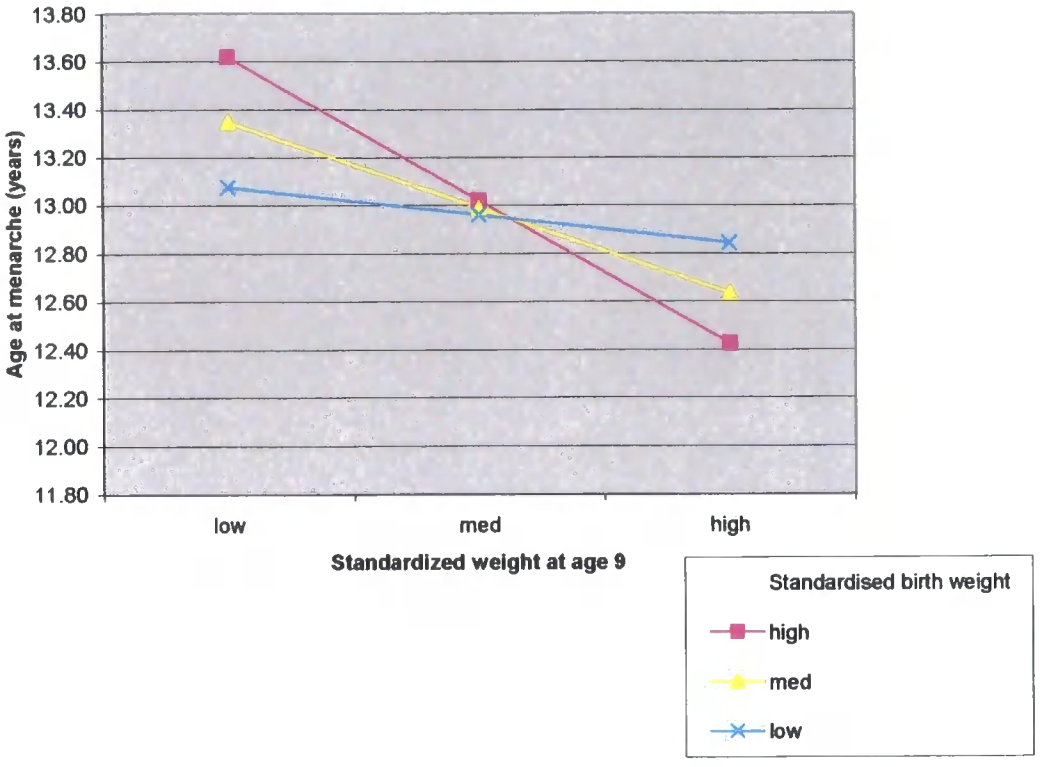
for low standardized birth weight (-1 SD) is

age at menarche= (-0.123721)* WAZ at 9 + 12.991 + 0.028* sds bw.

t= -0.47, p=0.64,

These slopes indicate that the weight of the association between age at menarche and standardized birth weight is different at different levels of standardized weight at age 9 however they are not significantly different. These equations are graphed in Figure 1.

Figure 1. Age at Menarche predicted by standardized birth weight and standardized weight at age 9



DISCUSSION

Principal finding

This analysis, using prospective and retrospective data from a longitudinal cohort study, found that the age at which participants experienced menarche was predicted by prenatal factors and childhood development. Two main independent associations were observed: girls who experienced a shorter gestation and girls who were heavier at age 9 had earlier menarche. Birth weight adjusted 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. For girls born small for gestational age, weight for age at age 9 did not strongly affect age at menarche, which was close to average. 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.

The null hypothesis of no association between early life experience and menarcheal age could not be rejected in the case of associations between the timing of menarche and rate of infection, the duration of breastfeeding, or socioeconomic indicators.

Ordinal logistic regression and multiple regression broadly showed the same results in each stage of analysis. Ordinal logistic regression results were generally less significant than multiple regression results which would be expected because of the loss of information that results from turning a continuous variable (menarche in months and years) into a categorical one.

Comparison with other studies

The age at menarche as recalled for this cohort (mean 12.94 years, median 13.00) was a few months earlier than found in cross sectional studies of menarcheal ages for girls born in the northeast of England in the mid-twentieth century. Studies of girls in Newcastle upon Tyne, Northumberland, and South Shields, County Durham found median ages at menarche of 13.3, 13.3, and 13.4 years respectively (Billewicz,

Fellowes and Thomson 1981; Roberts, Danskin, and Chinn 1975; Roberts, Rozner, and Swan 1971). These small differences in median menarcheal ages may be due to error in recall in the Thousand Families data or cohort effects for different birth years.

The results of this study lend credence to the idea that fetal conditions may influence the timing of menarche as an association between these was found. However, these results do not specifically accord with the emphasis on fetal growth rate, especially in mid to late gestation, found in Barker's explanation of his hypothesis (Barker 1995) and in the studies that support the Barker hypothesis.

The most similar cohort in time period and location to the Thousand Families Study which has looked at links between fetal conditions and age at menarche is the MRC National Survey of Health and Development (NSHD) cohort which includes all births in Britain in the first week of March, 1946. When Cooper et al (1996) investigated links between birth weight and menarcheal age in the MRC NSHD cohort they found significant associations between quintiles of birth weight and age at menarche and this relationship remained significant when relative weight at age 7 was controlled for (Cooper et al 1996). 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. Part of the difference in findings may be due to the different methods of standardizing birth weight. Both Cooper et al (1996) and dos Santos Silva et al (2002) use birth weight standardized against its own distribution rather than against growth charts or gestation which is unlikely to have been as accurate at isolating the effect of fetal growth rate as standardizing for gestational age. Indeed in the results from multiple regression in the present study, controlling for relative heaviness at age 9 produces a significant association between raw birth weight and menarcheal age. However, this effect appears to be due to differences in gestation length because when each effect is isolated gestation

becomes significant and birth weight for gestational age becomes non-significant in predicting menarcheal age.

Analysing data from the same cohort, dos Santos Silva et al (2002) found no significant relationship between standardized ranks of birth weight and age at menarche and found that rapid growth in infancy led to early menarche independently of birth weight. The authors attribute the difference between these findings and those of Cooper and colleagues (1996) to the fact that they have used multiple data points to assess patterns of growth in infancy and childhood.

In a Swedish study, Persson et al (1999) also showed that the positive association that they initially found between smallness for gestational age and the timing of menarche was due to early childhood growth, which they established by plotting a growth curve for each child from birth to six years. Persson et al (1999) did not find a relationship between the timing of menarche and tallness for gestational age, shortness for gestational age, largeness for gestational age or short gestation compared to normal infants. The lack of association between the timing of menarche and prematurity by Persson et al (1999) is not consistent with the findings of the current study.

A Norwegian study by Romundstad et al (2003) found a positive association between birth weight and age at menarche and the relationship remained after adjusting for length of gestation. These authors also found a positive association between thinness at birth as indicated by ponderal index and menarche (Romundstad et al 2003). However, ponderal index was not found to be associated with the timing of menarche (Romundstad et al 2003). Despite the completeness of their birth data these authors did not have measures of growth in childhood and could not investigate whether childhood growth confounded these relationships.

Adair (2001) found no relationship between menarche and birth weight alone in the Filipino cohort, however, thinness at birth was associated with early menarche. This effect is unmodified by measures of fatness at eight years and is strongest in girls with rapid growth in infancy (Adair 2001). Like the present study, Adair (2001) also found significant positive associations between menarche and gestational age in

several multivariable models, however she does not comment on this association in the text.

It is not clear why the length of gestation would be associated with the age at menarche though this has been found in at least one study that compared premature infants and controls for indices of growth and maturation (Bhargava et al 1995). The direction of the relationship between length of gestation and menarche in Bhargava and colleagues' analysis was the same as presented here.

Length of gestation is correlated with many factors including maternal age, mother's cervical length during pregnancy (Heath et al 1998; Goldenberg et al 2003), mother's nutrition during pregnancy (Herrmann et al 2001), mother's substance use during pregnancy including smoking (Shiao, Andrews, and Helmreich 2005, Little et al 2005), parental ethnic group (Badr, Abdallah, and Mahmoud 2005; Shiao, Andrews, and Helmreich 2005), presence of bleeding during pregnancy (Kim et al 2005), mother's stress level during pregnancy evidenced by mother's perception or endocrine characteristics (Hobel et al 1999; Ruiz, Fullerton and Dudley 2003), birth characteristics of mother's previous children (Mercer, Milluzzi, and Collin 2005), occurrence of maternal vaginal or intrauterine infection during pregnancy (Hillier et al 1995, Goldenberg, Hauth, and Andrews 2000), occurrence of maternal periodontal infection (Dörtbudak et al 2005), and presence of fibronectin in the cervix or vagina during pregnancy (Goldenberg et al 1996, Golden berg et al 2003).

The relationship between menarche and gestation length may be due to the effect of *in utero* hormonal exposure on the 'set point' negative feedback loop of the HPO axis or the effect of an *in utero* exogenous chemical exposure on this 'set point'. Thus, a key issue to consider is that the mechanisms underlying the relationships found here and in other studies are unclear and may well be due to independent factors affecting the pace and/or magnitude of fetal and childhood growth and development.

The lack of association between age at menarche and birth order fits with findings in other areas of the north east in this period (Roberts, Danskin, and Chinn 1975; Roberts, Rozner, and Swan 1971) but not with the previous finding in Newcastle

upon Tyne itself (Billewicz, Thomson, and Fellowes 1983). Similarly, the lack of a statistically significant association between menarcheal age and social class accords with the findings from Northumberland (Roberts, Danskin, and Chinn 1975) and South Shields (Roberts, Rozner, and Swan 1971) but not with the finding of Billewicz, Thomson, and Fellowes (1983) of a significant association in girls born in Newcastle upon Tyne in 1962. The time elapsed between the births of the participants in the Newcastle Thousand Families study and the births of the study participants in the later group from Newcastle may explain some of the difference in findings. The difference in how social classes were grouped for analyses may also account for the difference in results. Billewicz, Thomson, and Fellowes (1983) found their association using only two groups, manual and non-manual occupations. Also, social class was not recorded at the time of menarche but at other points in time including at birth and at age 5. As the strongest predictor of menarcheal age was related to weight at a time nearer to the mean age at menarche than age 5, it is possible that social class at later ages might have shown a relationship to menarcheal age. The lack of association may be due to the fact that social class at the time of menarche is not available for this cohort; however, as social class changed little from birth to age 5, it is unlikely that social class would have changed over the period between age 5 and achievement of menarche. In addition, Malina (1997) has suggested that there may be a 'window' in the period just before and after birth where environment (social or biological) can affect future reproductive function which would mean that later childhood social circumstances would not have affected affect reproductive maturation.

The lack of association between the timing of menarche and the rates of infection in early childhood in this cohort differ from the finding of Khan and colleagues (1996) that more illness was associated with delayed menarche. This difference may be a result of how illness over a period of time was calculated. Khan et al (1996) used the percentages of time spent ill with diarrhea and respiratory illnesses in the study period, whereas this study has 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. The difference could also be due to a relatively smaller burden of infection in childhood on these participants compared with the Guatemalan girls studied by Khan and colleagues (1996). Differences in nutrition, sanitation and

access to health care between rural Guatemala and Newcastle upon Tyne in the twentieth century may have influenced infection rates in children a great deal.

The strong independent predictive power of indicators of fatness in the years leading up to menarche on menarcheal age that was found in both multiple regression and ordinal logistic regression in this study accords with previous studies using various methods in many different populations (Petridou et al 1996; Koziel and Jankowksa 2002; Helm et al 1995; Vitalle et al 2003; Bharati and Bharati 1998; Chowdhury et al 2000; Hesketh, Ding, and Tomkins 2002; Cooper et al 1996; Adair 2001; Ersoy et al 2001; dos Santos Silva et al 2002; Freedman et al 2003; St. George, Williams, and Silva 1994; Anderson, Dallal, and Must 2003; Ayatollahi, Dowlatabadi, and Ayatollahi 2002). As discussed previously there are several plausible explanations for the association between measures of fatness and menarcheal age including direct effects of fat on the HPO axis (such as aromatisation of androgens into estrogens) and direct effects of the maturation of the HPO axis on fatness (via estrogens promoting fat storage).

The lack of association between menarcheal age and each of the height related variables does not support Ellison's hypothesis that height is the strongest predictor of menarcheal age (Ellison 1981a; Ellison 1981b). Cooper et al (1996) found an 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 survival model which included all participants. Analysis of childhood growth trajectories in the same cohort by dos Santos Silva et al (2002) found that change in ranks of height in infancy and childhood were positively associated with age at menarche which does lend support to Ellison's hypothesis. Thus, height velocity or measures of change in height z-scores taking into account more points in infancy and childhood, had these been calculable for this cohort, would have provided a truer test of Ellison's hypothesis.

Strengths and weaknesses of the study

No other studies have used breastfeeding duration, complete illness data, indicators of fetal conditions, and measures of growth in childhood to assess univariate and multivariable associations with menarcheal age. All the data except menarcheal age

were collected prospectively. Measures of height and weight at ages other than 9 and birth were available for smaller numbers of the women for whom age at menarche was available, however it was too incomplete to have been of use. More complete multiple measures of weight and height in childhood would have allowed a clearer picture to be drawn of the effect of the rate of growth relative to the starting point of each child on menarcheal age. Other measures of fetal growth and nutrition (placental to fetal weight ratio, ponderal index, or data collected through ultrasonography) might have shown associations with menarcheal age or might have illuminated the underlying cause of the association between menarche and gestation length. An obvious weakness of these data is that age at menarche was collected retrospectively approximately 37 years after the event which has affected both the number of participants and recall (see appendix). Loss to follow-up between childhood and middle age has made the sample smaller than it would have been if menarcheal age had been collected prospectively. However, the present sample comprises 49.1% of the original sample of female participants in the Thousand Families Study. This high rate of participation in the follow-up was achieved by inclusion of cohort members who had moved out of the region. Those who completed the questionnaire for the age 50 follow-up in which the question about menarcheal age appeared have been shown to be not significantly different from the original cohort in any of the variables related to birth, infancy and childhood (Pearce et al 2004).

The problems inherent in using data that may be affected by error in recall have been partially overcome by the use of menarcheal age as a categorical variables; however, it is not clear what effect error in recall may have had on testing the hypotheses in this work, though they may have weakened the power of the analyses.

CONCLUSION

This study lends support to hypotheses that greater childhood tissue growth is associated with earlier menarche which in turn supports the hypothesis that reproductive maturation is responsive either to the childhood circumstances that promote or delay growth or to growth in childhood itself in order to achieve fecundity at a time when successful gestation is likely. This study also supports the hypothesis that fetal conditions are associated with the timing of menarche. Though gestation length has not been the 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 study (Adair 2001). It would seem that Malina's (1997) suggestion that the 'window' where early life can influence menarcheal timing closes in early infancy has not been borne out by these data since the strongest association found was between weight standardized for age at 9 and menarcheal age. However, the interaction effect that has been found in this study lends some support in that there may be a 'window' where fetal and perinatal conditions affect the 'set-point' of the HPO axis and thus later growth may have different effects on reproductive maturation because of this 'set point'. 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.

APPENDIX

The validity of age at menarche self-reported in adulthood

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Summary

Background

There is an increasing use of measures of childhood characteristics that are retrospectively recalled in adult life. The validity of such measures, including age at menarche, need to be assessed and factors that influence accuracy of recall examined.

Methods

Using data on up to 1050 women from the MRC National Survey of Health and Development, the validity of age at menarche self-reported at age 48 years was assessed by comparing this with age at menarche recorded at age 14/15 years. This was done by calculating limits of agreement, kappa (κ) statistic and Pearson's correlation coefficients (r). The effect of socioeconomic position, education, experience of gynaecological events and psychological symptoms on agreement between the two measures of age at menarche was investigated using logistic regression.

Results

At best the validity of age at menarche self-reported in middle-age compared to age at menarche recorded in adolescence was moderate ($\kappa = 0.35$, $r = 0.66$, $N = 1050$). Validity was improved by categorising age at menarche into three groups: early, normal and late. Agreement was influenced by educational level and having had a stillbirth or miscarriage.

Conclusions

The level of validity shown in this study throws some doubt on whether it is

justifiable to use age at menarche self-reported in middle-age. Given it is likely to introduce error and bias it is important that researchers are aware of these limitations and use such measures with caution.

Keywords: Age at menarche; validity; self-reported measures; life course epidemiology

Introduction

Menarche heralds the beginning of a female's reproductive life and its timing is an indicator of the start of regular exposure to endogenous oestrogen and other hormones. Age at menarche is predicted by a number of factors including childhood growth and weight(1;2) and has been found to be associated with a range of diseases in adulthood including breast cancer,(3) depression(4) and rheumatoid arthritis.(5) It is therefore a widely used measure in epidemiological and anthropological studies, considered as an outcome, predictor, confounder, effect modifier or mediator.

The growth of interest in a life course approach to adult health(6) means that studies which were not initiated until study participants were already adults or are historical cohorts which have been revitalised after a period without data collection, often rely on participants' recall of a range of earlier life factors. There is a need to validate these retrospective measures as they may be more prone to measurement errors and bias than prospectively collected measures.

Previous studies that have assessed the validity of age at menarche recalled in adulthood have had small sample sizes (current studies include between 43(7) and 368 women(8)), may not be generalisable as they use either unrepresentative study

populations(9) or have high loss to follow-up(10) and, have not investigated the characteristics which might account for variation in accuracy of recall.

The Medical Research Council National Survey of Health and Development (MRC NSHD) has information on age at menarche from two data collection points, one in adolescence and one in middle-age, and so presents an opportunity to examine the validity of age at menarche self-reported in middle-age and, to investigate whether a range of factors may influence this.

Methods

The MRC NSHD is a socially stratified, prospective cohort of 2547 women and 2815 men who have been followed up regularly since their births in March 1946. Data on a wide range of developmental, health and social factors across the life course have been collected during home and school visits and via postal questionnaires.(11)

During medical examinations performed when cohort members were aged 14 or 15 years, school doctors established, usually in the presence of at least one parent, whether the female members of the cohort had started their periods and if so, the month and year of onset of the first period. If a cohort member had not reached menarche by the time of the interview this was recorded. All female members of the cohort were again asked in 1994, aged 48 years, in one of a series of annual postal questionnaires sent to them, for the age in years at which their periods started (phrased "How old were you when you had your first menstrual period?" followed by a blank space and the word "years").

By 1993, 154 (6.0%) of the original female cohort members had died, 232 (9.1%) were abroad and not contacted, 296 (11.6%) had refused to participate in the study and 87 (3.4%) were untraced. Of the remaining 1778 women, 1382 (77.7%) returned the relevant questionnaire in 1994, of whom 1050 had both measures of age at menarche recorded (n=946) or had an age at menarche reported at age 48 years and were known not to have reached menarche by the time of their interview at age 14/15 years (n=104). The data on these 1050 women were used to assess the validity of the measure of age at menarche self-reported in middle-age. All analyses used age at menarche in completed years since a more accurate timing was not available for the age self-reported in middle-age.

To assess factors which it was thought could influence validity of recalled age at menarche, two measures of social class, one in childhood and one in adulthood, and a measure of educational attainment, all collected prospectively, were used. Father's occupational social class at age 11 years (or at age 15 or 4 years if missing at age 11 years (n= 68)) and own occupational social class at age 53 years (or at age 43, 36, 26 or 20 years if missing at age 53 years (n=174)) were the two measures of social class. Both measures were classified according to the Registrar General's classification and grouped into three categories: I or II; III Non-manual or III Manual; and IV or V. Educational level achieved by age 26 years was grouped into five categories: Degree or higher; 'A' levels or equivalent; 'O' levels or equivalent; CSE, clerical course or equivalent; None. To assess the effect of having experienced a gynaecological 'event', hysterectomy and oophorectomy status and experience of a stillbirth or miscarriage were used. Women were asked to report any operations to remove their uterus and/or ovaries at home visits which took place at ages 43 and 53 years and in a

series of postal questionnaires sent annually between the ages of 47 and 54 years and at 57 years. As age at menarche was recalled at age 48 years three categories of hysterectomy/oophorectomy status were created: no hysterectomy or oophorectomy; hysterectomy and/or oophorectomy before age 48 years; hysterectomy and/or oophorectomy at age 48 years or later. At age 43 years women were asked during a home visit whether they had ever experienced a stillbirth or miscarriage. This characteristic was coded as a binary variable. Finally, to assess the effect of psychological distress on agreement, a 12 point scale(12) based on four psychological symptoms (anxiety/depression, irritability, tearfulness and panic) reported by women for the previous 12 months in the postal questionnaire at age 48 years (the same age as age at menarche was recalled) was used. The choice of symptoms was based on a factor analysis of 20 common health symptoms, and the score reflected how bothersome each was in everyday life: not had symptom (score 0), had symptom but not bothered (score 1), bothered a little (score 2), bothered a lot (score 3).(12)

Statistical methods

Using data on the 946 women who had reached menarche by the time of their interview in adolescence 95% limits of agreement(13) and a Pearson's correlation coefficient were calculated. To calculate the limits of agreement the difference between the two measures of age at menarche was calculated (by subtracting the age reported in middle-age from age recorded in adolescence for each woman) and a plot made of these differences against the mean of the two measures to check that there was no relationship between them. After also checking that the differences were normally distributed, the mean and standard deviation (SD) were used to calculate

the 95% limits of agreement i.e. mean difference $\pm$ (1.96 x SD). In further analyses, including the 104 women who had not reached menarche by the time of their interview in adolescence, age at menarche was considered in individual years up to and including age 13 with menarche reported at age 14 years or above grouped together. These two measures of age at menarche were cross-tabulated, a kappa (κ) statistic was used to assess the level of agreement and a Pearson's correlation coefficient was calculated. To examine whether categorising age at menarche improves validity, age at menarche was categorised into three groups: early menarche ($\leq$ 11 years); normal menarche (12 – 13 years); late menarche ($\geq$ 14 years). The two categorical measures of age at menarche were cross-tabulated and agreement assessed using κ. Logistic regression was used to examine whether there was an association between agreement (yes or no) between the two categorical measures of age at menarche and childhood and adult social class, education, gynaecological events and psychological symptoms. All analyses were performed using Stata version 8.2.

Results

Of the 946 women with a valid age at menarche at both measurement points, 412 (43.6%) had recalled exactly the same age at menarche (in years) at age 48 years as had been recorded during the medical examination at age 14/15 years (see table 1). There were 195 (20.6%) women who recalled an age at menarche in middle-age only one year higher than their age at menarche recorded in adolescence and a further 199 (21.0%) women who recalled an age at menarche one year younger, suggesting that there was no systematic under or over-reporting of age at menarche in middle-age. The 95% limits of agreement were -2.19 to 2.15 years indicating that 95% of women

reported an age at menarche in middle-age which differed by no more than 2.2 years in either direction from their age at menarche recorded in adolescence. Pearson's correlation coefficient (r) was 0.59. In analyses including all 1050 women with ages at menarche at or above 14 years grouped together, 527 women (50.2%) had recalled the same age at menarche in completed years at age 48 years as had been recorded during the interview at age 14/15 years. $\kappa = 0.35$ ($p < 0.001$) which indicates fair agreement between the two measures.(14) Pearson's correlation coefficient was 0.66.

Table 1: Cross-tabulation of reported age at menarche (in years) ascertained during adolescence and in middle-age in the MRC NSHD (N = 1050)

Age at menarche (yrs) – recorded at age 48 years	N (column %) Age at menarche (yrs) – recorded at age 14/15 years							Total
	9	10	11	12	13	14	Not yet reached	
9	1 (14.3)	0 (0.0)	4 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5
10	2 (28.6)	10 (43.5)	16 (11.4)	14 (4.7)	9 (2.5)	1 (0.8)	0 (0.0)	52
11	2 (28.6)	7 (30.4)	80 (56.7)	85 (28.2)	36 (10.1)	1 (0.8)	0 (0.0)	211
12	2 (28.6)	3 (13.0)	27 (19.2)	113 (37.5)	67 (18.9)	3 (2.5)	1 (1.0)	216
13	0 (0.0)	1 (4.3)	12 (8.5)	60 (19.9)	146 (41.1)	31 (26.1)	9 (8.7)	259
14	0 (0.0)	0 (0.0)	2 (1.4)	21 (7.0)	79 (22.3)	62 (52.1)	26 (25.0)	190
15	0 (0.0)	1 (4.3)	0 (0.0)	7 (2.3)	14 (3.9)	20 (16.8)	39 (37.5)	81
16	0 (0.0)	1 (4.3)	0 (0.0)	1 (0.3)	4 (1.1)	1 (0.8)	20 (19.2)	27
17	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (5.8)	6
18	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1
19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.9)	2
Total	7 (100)	23 (100)	141 (100)	301 (100)	355 (100)	119 (100)	104 (100)	1050

Note: The figures shaded are those where the two measures are in agreement.

When age at menarche was grouped into three categories (≤ 11, 12-13, ≥ 14), 685 women (65.2%) were assigned to the same category by both measures (see table 2). $\kappa = 0.43$ ($p < 0.001$) which indicates moderate agreement.(14)

Table 2: Cross-tabulation of categories of age at menarche derived from ages of menarche ascertained during adolescence and in middle-age in the MRC NSHD (N = 1050)

Age at menarche (yrs) – recorded at age 48 years	N (column %) Age at menarche (yrs) – recorded at age 14/15 years			Total
	≤ 11	12 – 13	≥ 14	
≤ 11	122 (71.3)	144 (22.0)	2 (0.9)	268
12 - 13	45 (26.3)	386 (58.8)	44 (19.7)	475
≥ 14	4 (2.3)	126 (19.2)	177 (79.4)	307
Total	171 (100)	656 (100)	223 (100)	1050

Note: The figures shaded are those where the two measures are in agreement.

No association between childhood social class and agreement between the two categorical measures of age at menarche was found (see table 3). In unadjusted analyses there was greater agreement amongst the more educated women and women in the most advantaged social classes (p=.03 in both cases) compared with less educated women and women in the least advantaged social classes. The effect of adult social class was attenuated after adjustment for education and childhood social class whereas the effect of education remained on the borderline of conventional significance after mutual adjustment. The results presented in table 3 include only those women with complete data on all three social and educational measures (N=999), however, there was no difference in the findings from unadjusted analyses including the total available sample (results not shown).

Table 3: Tests of the association between agreement and socioeconomic and education characteristics (agreement is when a woman is placed in the same age at menarche category (early, normal or late) by both measures) N=999

Characteristic	Agreement between the two measures		Unadjusted OR (95% CI) (N=999)	p†	Adjusted OR* (95% CI) (N=999)	p†
	Yes (n = 657) (N (%))	No (n = 342) (N (%))				
Father's social class						
I or II	167 (65.0)	90 (35.0)	1.00	0.89	1.00	0.28
IIINM or IIIM	328 (65.6)	172 (34.4)	1.03 (0.75, 1.41)		1.20 (0.86, 1.68)	
IV or V	162 (66.9)	80 (33.1)	1.09 (0.75, 1.58)		1.39 (0.92, 2.08)	
Own social class in adulthood						
I or II	255 (70.1)	109 (30.0)	1.00	0.03	1.00	0.15
IIINM or IIIM	292 (65.2)	156 (34.8)	0.80 (0.59, 1.08)		0.83 (0.60, 1.17)	
IV or V	110 (58.8)	77 (41.2)	0.61 (0.42, 0.88)		0.66 (0.44, 1.01)	
Highest educational attainment						
Degree or higher	42 (77.8)	12 (22.2)	1.00	0.03	1.00	0.06
'A' levels or equivalent	161 (66.3)	82 (33.7)	0.56 (0.28, 1.12)		0.56 (0.28, 1.13)	
'O' levels or equivalent	191 (70.2)	81 (29.8)	0.67 (0.34, 1.35)		0.71 (0.34, 1.47)	
CSE, clerical course or equivalent	54 (57.5)	40 (42.6)	0.39 (0.18, 0.83)		0.40 (0.18, 0.91)	
None	209 (62.2)	127 (37.8)	0.47 (0.24, 0.93)		0.50 (0.24, 1.05)	

† p-value from likelihood ratio test

* adjusted for the two other variables shown in the table

There was no association between the psychological symptom score and agreement between the two categorical measures of age at menarche (results not shown). There was greater agreement among the women who had experienced a stillbirth or miscarriage compared with women who had not (see table 4). However a similar association was not seen by hysterectomy/oophorectomy status. Adjusting for education did not change these findings.

Table 4: Tests of the association between agreement and gynaecological events (agreement is when a woman is placed in the same age at menarche category (early, normal or late) by both measures) N=1050

Gynaecological event	Agreement between the two measures		Unadjusted OR (95% CI)	p†
	Yes (n = 685) (N (%))	No (n = 365) (N (%))		
Ever had surgery to remove uterus and/or ovaries				
No	529 (66.5)	266 (33.5)	1.00	0.18
Yes (age < 48 years)	106 (63.5)	61 (36.5)	0.89 (0.62, 1.26)	
Yes (age ≥ 48 years)	50 (56.8)	38 (43.2)	0.65 (0.42, 1.03)	
Ever had a stillbirth or miscarriage				
No	476 (63.4)	275 (36.6)	1.00	0.01
Yes	165 (72.4)	63 (27.6)	1.51 (1.09, 2.10)	
Missing	44 (62.0)	27 (38.0)	-	

† p-value from likelihood ratio test

The 1050 women included in the analyses were significantly more likely to have a higher adult social class and more formal educational qualifications than the 1497 women who were not included due to death, refusal to participate, being abroad or lost, or failing to answer both relevant questions (p=0.001 and p<0.001 respectively).

Discussion

Principal findings

The results of this comparison suggest that there is only at best, moderate agreement between two measures of age at menarche, one collected in adolescence, the other in middle-age. When all the available data were included (n=1050) and age at menarche at age 14 years or above was necessarily grouped, which we would expect to overestimate the true level of validity, level of agreement (κ = 0.35) and the correlation (r=0.66) between the two measures was only moderate. Our results therefore suggest that age at menarche self-reported in middle-age is not very accurate. However, categorising age at menarche into three groups (early, normal and late) improved agreement (κ=0.43). Agreement between the two measures of age at menarche was influenced by educational level and having experienced a stillbirth or miscarriage. It may be that women who have a stillbirth or miscarriage will have had more reason to acquire accurate information as part of providing or understanding their gynaecological history.

Comparisons with other studies

A number of previous studies have examined the validity of retrospectively reported age at menarche.(7-10;15-18) The five studies with a similar length of recall to that considered in this study,(7-10;15) all of which are American, have comparable results. In one study age at menarche was accurately recalled by 59% of women (N=160).(9) In the four other studies, comparisons of recalled measures with prospective measures of age at menarche, produced correlation coefficients of 0.60 (N=143),(15) 0.67 (N=50),(10) 0.75 (N=43)(7) and 0.79 (N=368).(8) Differences in results between the studies could be attributable to a number of factors including: differences in the

characteristics of the study populations; variation in the length of recall; differences in the method by which women were asked to recall age at menarche (i.e. face-to-face interview, postal questionnaire, supervised self-completed questionnaire) and; whether the women were asked to recall their age at menarche in years or in years and months.

Strengths and limitations

There are a number of limitations to this study. First, age at menarche reported during the medical interview at age 14/15 years was still subject to recall error because it was not collected at the time of the event. Second, there was a group who had not reached menarche by the time of that interview. This would only be a major limitation if there was variation in accuracy of recall by age at menarche but there was no evidence to suggest this. Third, the question on age at menarche posed in middle-age asked for women to report their age at menarche in years and so we were not able to assess the validity of recall of a more precise timing of menarche (i.e. by month and year). Fourth, the sample with complete data (n=1050) were more educated and from a higher social class than those with missing data (n=1497). However, there is no obvious reason why the relationship between educational attainment and recall accuracy would differ in these two groups.

This study has three important strengths. First, we evaluated the validity of age at menarche recalled retrospectively using limits of agreement and kappa as well as Pearson correlation coefficients. The majority of other studies(7;10;15) focus only on correlation coefficients, which are tests of association rather than agreement.(12;13) Second, we investigated factors that might influence accuracy of recall of age at

menarche which no previous study has done. Third, our results are likely to be more generalisable than those from other studies because of the larger sample size and the representativeness of the population from which the study sample is drawn.(19)

Implications for epidemiological studies using recalled age at menarche

The level of validity shown in this study throws some doubt on whether it is justifiable to use age at menarche in years self-reported in middle age. The level of agreement in the general population may be lower than our results suggest, given the association between educational level and accuracy of recall, and the over-representation of educated women in our responding sample in mid-life. We suggest that categorising data will improve validity, although this may still be subject to bias by educational status and having had a stillbirth or miscarriage. When designing questionnaires which ask study participants to recall the timing of events, researchers should consider using methods (e.g. comparison with peers) which may elicit more accurate responses than are gained by asking one simple question about timing.

We had expected that age at menarche, an event usually of some significance for women, would be accurately remembered. As it is not, our findings have wider implications for the validity of other measures in earlier life retrospectively recalled many years later.

Contributions: DK and MSP conceived the idea for the study. RC and MB planned and ran the analyses with supervision from RH, DK, SB, TMP and MSP. RC with input from MB drafted the paper and all authors commented on this and contributed to the final version.

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Ethical approval:

Relevant ethics committee approval was received for this study.

Competing interests: None declared.

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