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Birth weight, childhood growth and menarche in South Africa

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Birth weight, childhood growth and menarche in South Africa

by

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A research report submitted to the Faculty of Health Sciences,

University of the Witwatersrand, Johannesburg,

In partial fulfilment of the requirements for the degree of Master of Medicine in

Obstetrics and Gynaecology

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DECLARATION

I Frances Paterson, declare this research report to be my own work. It is being submitted for the degree of Master of Medicine in the branch of Obstetrics and Gynaecology in the University of the Witwatersrand, Johannesburg. It has also been submitted to the Colleges of Medicine of South Africa in partial fulfilment of the requirements for the qualification of Fellowship of the College of Obstetrics and Gynaecology

Frances Paterson

ABSTRACT

Background and objectives

Menarche serves an important marker of female health for individuals and populations. It indicates the onset of sexual maturation and reproductive capacity, but also serves as a prognostic factor for future growth, development, and the health of the individual and the population as a whole. Birthweight and childhood growth are thought to affect the age at menarche (AAM) through a number of different mechanisms but this relationship has yet to be fully explored. The objectives of this study were:

1. To describe the age of onset of menarche in a population of healthy 'normal weight' females in the Birth to Twenty cohort.
2. To demonstrate the influence of birth weight on the age of menarche
3. To assess the impact of childhood growth on the age of menarche
4. To assess the contribution of weight gain during specific periods in infancy and childhood on the age of menarche.

Design, setting and participants

Data from 788 South African children from the Birth to Twenty (Bt20) prospective birth cohort study who were followed prospectively throughout childhood were used. Variables included prenatal characteristics, birth measurements, serial measurement of height and weight during childhood, socio-economic status, and age at menarche. Exposures were weight at birth, then at 2 years, and 4 years; and conditional weight gain (CWG) between these ages. Outcome was age at menarche.

Results:

Age of onset of menarche: The average age of menarche in our sample was 12.66 years.

Relationship between birthweight on age of menarche: The findings of this study show that birthweight does not significantly affect AAM

Childhood growth and menarche: Our analysis shows a sustained and significant relationship between weight at 2 years, and weight at 4 years of age, with growth in the first 24 months having the greatest effect

Conclusion:

Increased weight gain in infancy during the first 24 and 48 months is associated with earlier AAM in girls. This has major implications for clinical practice especially in developing countries. There is currently a poor understanding of the underlying mechanisms underlying this phenomenon, and more research in this area is required to understand the interplay between environmental and genetic factors affecting the antenatal environment, childhood growth, and menarche.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
AAM	Age at menarche
Bt20	Birth to Twenty cohort study
CWG	Conditional weight gain, deviation from expected weight gain
LH	Luteinising hormone
FSH	Follicle stimulating hormone
GnRH	Gonadotropin releasing hormone
SNP	Single nucleotide polymorphism
SES	Socioeconomic status
LBW	Low birth weight
SGA	Small for gestational age

1 LITERATURE REVIEW

1.1 INTRODUCTION

The change in the age of menarche and its associated factors are of concern to the medical fraternity as adolescent reproductive health can have far reaching medical and psychosocial consequences. Early onset menarche has been related to cardiovascular and metabolic diseases, increased risk of breast cancer, depression, and increased all-cause mortality. Delayed onset menarche has, in turn, been linked to low bone density, fractures, and depression[(1),].

The influence of early life events on reproductive health and disease is currently not well understood. An appreciation of the fundamental pathways underlying human reproduction and reproductive disorders is essential as, it has implications for health and reproduction both on an individual and population scale.

The role of birthweight and childhood growth on the timing of menarche will enable a better understanding of the mechanisms involved, and help in the identification of possible periods at which intervention is feasible.

1.2 CONCEPTUAL FRAMEWORK

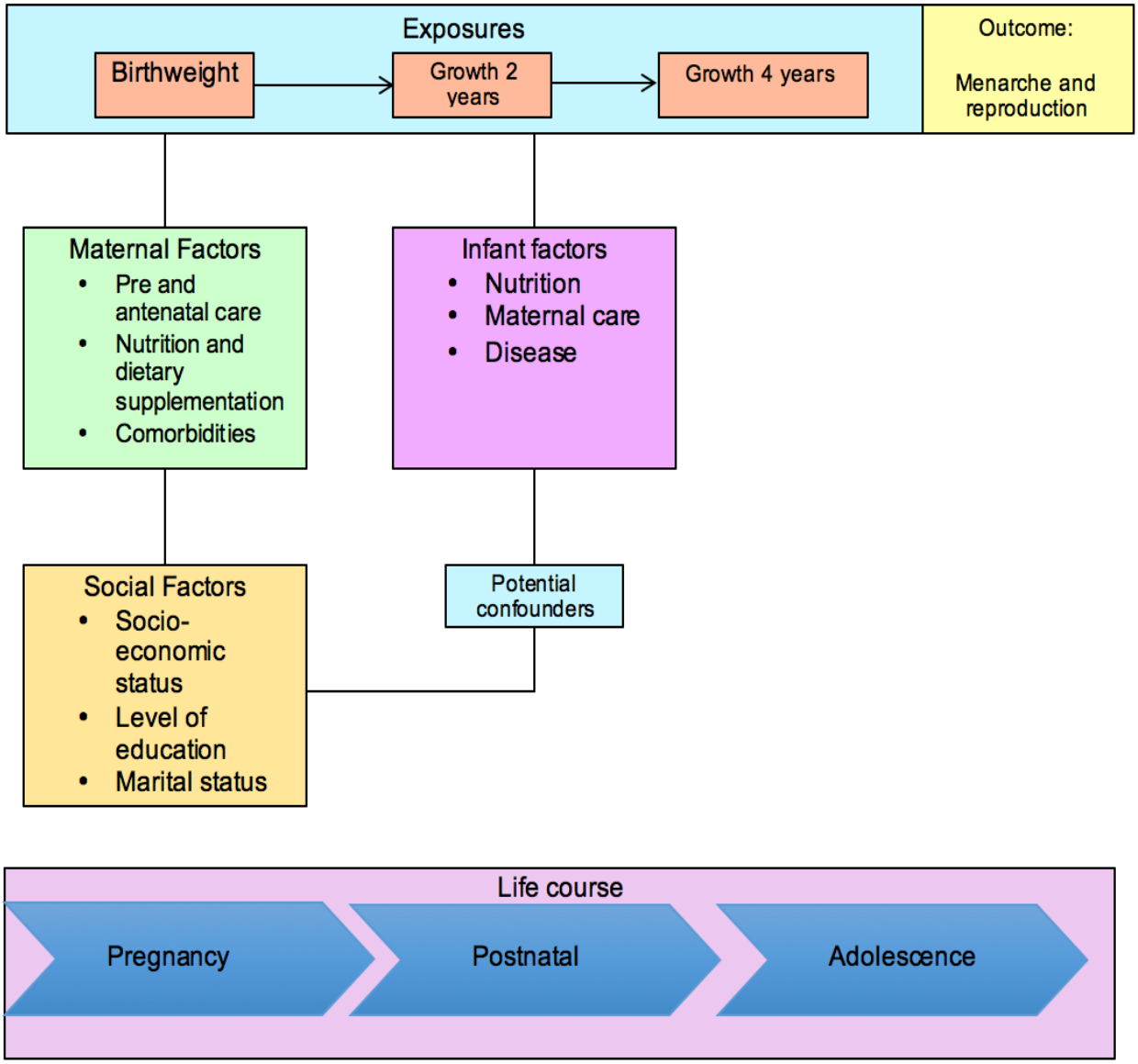


Figure 1 Conceptual framework of hypothesized relationships between birthweight, childhood growth and menarche. Constructed using the Lancet model from the Lancet Series on Maternal and Child Nutrition (2)

1.3 REPRODUCTION AND MENARCHE

Puberty is a phase in human reproductive development beginning with the inception of secondary sexual characteristics and ending with the onset of ovulation. One of the most pivotal events in the process is menarche, defined as the first menstrual period.

At the time of delivery, human females already have a predetermined, finite number of viable follicles, of approximately one million. During childhood, follicular atresia and apoptosis continues resulting in only 300 000 - 500 000 remaining at the time of menarche.

During pregnancy, mid-trimester fetal serum levels of the gonadotrophins luteinising hormone (LH) and follicle-stimulating hormone (FSH) are equivalent to adult female concentrations. These levels decrease as the pregnancy continues due to the negative feedback effect of increasing levels of oestrogen and progesterone. Following delivery and decrease of placental hormone production, gonadotropin levels again rise to adult levels within three months. For approximately eight years subsequent to this the hypothalamus and pituitary is highly sensitive to the negative feedback system due to very low serum oestrogen levels, as well as an innate central inhibitory effect on gonadotropin-releasing hormone (GnRH), resulting in diminished LH and FSH concentrations.

Normal pubertal timing would therefore necessitate specific changes in regulation of the hypothalamic - pituitary- ovarian axis, namely a concurrent reduced sensitivity to the feedback inhibition of oestrogen, and a decline in the intrinsic suppression of GnRH. Once appropriate oestrogen

concentrations have been reached, usually around mid-puberty, proliferation of the endometrium and menarche occurs[3].

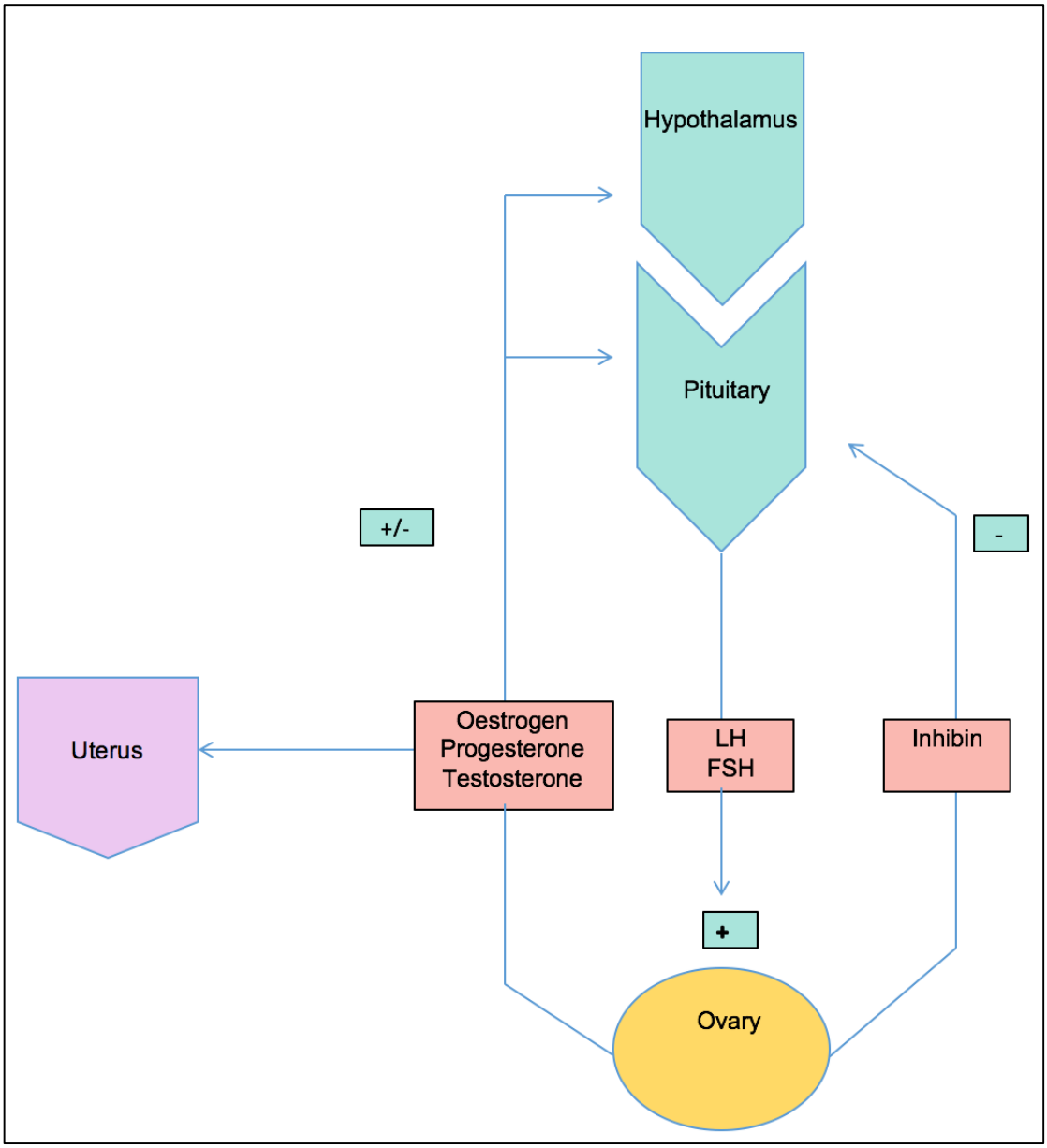


Figure 2 The female reproductive axis adapted from Williams textbook of Gynecology (4).

The age of onset of menarche is influenced various environmental and genetic factors as will be discussed in detail later in the literature review. Girls in developed countries in well nourished populations experience menarche at an average age of 12.43 years with a range between 12 and 13 years[5].

South African data published in 2009 has demonstrated a mean menarcheal age of 12.4 years for black, and 12,5 years for white girls respectively [6]. It is important to note, however, that there is a considerable range about the mean, and that menarche may equally normally occur between the ages of 10 and 18 without any underlying pathology[7].

That being said, menarche is not the only change occurring during puberty, and any deviation from the norm must be looked at as a part of entire clinical presentation. Therefore, as a rule, failure to menstruate by the age of sixteen years or later in the presence of concurrent secondary sexual characteristics is termed delayed menarche or primary amenorrhoea[3,7]. Unlike precocious puberty, early menarche is a poorly defined entity, perhaps because of the discrepancies noted in pubertal norms between different populations and the secular trend in menarche. Most studies nevertheless agree that menarche normally occurs after the age of ten at the earliest, with only 10% of females worldwide menstruating at 11.1 years of age[5].

1.3.1 Factors affecting menarche

Age at menarche is multifactorial, and is influenced by both environmental and genetic factors.

Phenotypically, the genetic influence on menarche can also be illustrated by the difference in the average age of menarche exhibited between different races. Even when findings were adjusted for body mass index (BMI) differences, it has been shown that African- American girls start their menses a significant time before those of other races. A study conducted over twenty years in Bogalusa, Louisiana, observed that menarche in black girls began on average three months earlier than in white girls (12.3 versus 12.6 years). In

addition, the study noted a median decrease in menarcheal age of approximately 9.5 months in black girls over the 20 year study interval, while a much smaller and less consistent decrease of two months was apparent in the white subjects[8]. Another study, conducted using data from the Third National Health and Nutrition Examination Survey found onset of menarche at 12.1 years for black girls; 12.2 years for Mexican American girls; and 12.7 years for white girls[9]. The findings of a 2009 South African study found a statistically significant secular trend in black girls only. The authors concluded that the lack of significant difference between the two races and and the fact that a secular trend was found only in black girls to be a reflection of the socioeconomic differences between the two groups[6].

One of the first genetic loci to be identified as having an influence on menarche was the LIN28B. Genes from this locus are thought to influence the timing of breast development in girls, as well as the onset of pubic hair growth in boys. It is also thought to play a pivotal role in the programing of the pubertal growth spurt in both sexes[10]. A second locus involved in the timing of menarche was discovered in an intergenic region at 9q31.28,10. Together, however, the above two loci can only explain 0.6% of the variance in the age of menarche. More recently, numerous other loci have come into focus as having a role to play in the determination of age of menarche. A recent study published in Nature Genetics 2010 has found approximately thirty additional loci on the human genome believed to have some control over AAM. Interestingly, among these are included four loci already known to be associated with BMI (in or near FTO, SEC16B, TRA2B and TMEM18), three in or near genes thought to be related to hormonal regulation pathways

(INHBA, PCSK2 and RXRG), and three in or near genes with ties to energy homeostasis (BSX, CRTC1 and MCHR2)[10]. Other studies have shown that single nucleotide polymorphisms (SNP) of genes such a CYP17, which plays a key role in estrodiol formation; and the IGF1 gene (SNP rs6124 on exon 4) may also influence AAM[11,12].

The environmental influences on menarche are equally as varied, and begin prenatally and continue postnatally up to menarche. The study of these factors is confounded as many of them seem to interact with each other and the mechanisms underlying these interactions is poorly understood.

The impact of the environment on an individual is thought to begin as early as intrauterine life. The fetal origins hypothesis is based on the postulation that fetal adaptations to the intrauterine environment may result in permanent alteration of fetal structure, physiology, and metabolism, possibly predisposing that individual to chronic disease later in life. These maladaptions include persisting alterations in the way cholesterol is metabolised, blood pressure changes, abnormal insulin release, and a change in a wide variety of other endocrine, metabolic and immune functions. It is believed that these modifications ultimately lead to diseases with serious consequences for morbidity and mortality such as coronary heart disease and diabetes[13,14].

Recent developments in the study of developmental plasticity and life history biology have led to a better understanding of the responses of a developing organism to environmental signals. There are one of two possible adaptive intrauterine responses which can affect the AAM, one which provides immediate advantage, and one which provides delayed advantage[15]. The benefit of an instantaneous reaction to an adverse environment is intrauterine

survival, but there may be a compromise between this immediate advantage and its long-term sequaelae. An example of this is the undernourished fetus. When a fetus is chronically undernourished in-utero, changes may occur to program the structure of tissues and organs to favour the fetus in its current environment. However, these changes may actually be deleterious in the long term and lead to increased morbidity and mortality later in life[15,16].

The second adaptation to environmental stressors is via a delayed response, with the initiation of a chain of events allowing for an adaptive trait that manifests itself only later in life. Following from the previous example of an undernourished fetus, the developing organism analyses its current nutritional environment, and in anticipation of the same environment in the future, makes physiological adjustments as a consequence. This strategy is based on the fact that gene transmission is ensured by earlier maturation. The trade-off with this adaptation method is that, should the predicted future deprivation not materialise and a more abundant postnatal environment ensue, metabolic compromise and morbidity may follow. The basis for the adaptations described above are epigenetic changes, which alter or modify the genetic settings for the control of metabolic homeostasis[15].

Given its relevance to this study, an entire chapter will be dedicated to the discussion of birth-weight and childhood growth which would normally follow the discussion of intrauterine factors.

1.3.2 Early menarche

Early menarche has been associated with various exposures and psychosocial factors. Maternal comorbidities and/or exposures such as diabetes, gestational hypertension, prenatal exposure to cigarette smoke, and

diethylstilbestrol (DES) exposure have been linked to earlier AAM[16,17]. DES is one of a multitude of endocrine-disrupting chemicals (EDCs), a group of environmental chemicals which have become a major focus in the study of puberty in recent years. Their general use is in industry as industrial solvents or lubricants (polychlorinated biphenyls [PBB's]), plastics (Bisphenol A) fungicides/pesticides (vinclozolin/dichlorodiphenylthrichloroethane), or pharmaceutical agents (DES). Some EDC's are structurally similar to oestrogen, while others interact with androgen receptors. While their mechanism of action may be varied, the negative impact they have on the endocrine system remains clear. Specifically, Phthalates and PBB's have been implicated in earlier AAM and breast development[18]. Other early life exposures associated with earlier menarche include young maternal age at index birth, and firstborn status[16].

Anthropomorphic indices, such as weight, height or BMI, also have a strong effect on AAM.

The first theories linking menarche and BMI were put forward in the early 1970s by Frisch and Revelle, who first proposed the idea of the 'critical' body weight necessary for the onset of menses. The evolutionary reason behind the link between body weight and menarche may be to guarantee that pregnancy cannot occur without the presence of adequate energy stores to maintain mother and fetus[19]. Extending that theory, researchers have now found that an increased BMI in mid- childhood is also associated with early menarche[18,20,21]. This suggests that the worldwide obesity epidemic may in part account for the secular trend in menarche, and the accompanying decreasing age in breast development, although this is subject to some

debate. However, not all academics are convinced that obesity itself is responsible for the early menarche seen in girls with a raised BMI. A study conducted in Dunedin, New Zealand found that taller, heavier girls with a raised BMI at age 7 reached earlier menarche than their contemporaries. They concluded that height had the greatest influence on age at menarche, a finding that has been confirmed by two other studies[18,22].

With regards to nutritional habits, it is not food quantity alone, but food quality that influences AAM. Higher energy-adjusted food consumption has been linked to early menarche and it has also demonstrated that a higher animal protein to vegetable protein ratio in early childhood is associated with early menarche, even after controlling for BMI[18].

The psychosocial factors related to early puberty include the 'life-setting', i.e. family size, parental education, and income. For example, girls growing up in urban environments have earlier AAM than their rural counterparts[18]. The socio-economic milieu in which girls are raised also has an impact on menarche. Many studies report a direct relationship between AAM and low socioeconomic status (SES)[18,23,24]. The mechanism through which SES affects AAM is not well understood, but may be linked to childhood obesity, which can be more prevalent in low socioeconomic groups[25].

Another theory is the 'stress hypothesis' theory which postulates that parental absence could lead to low SES, which leads to exaggerated stress levels, which in turn lessens the AAM[23]. Seemingly counter-intuitively, higher parental income is also associated with earlier menarche[18]. Male presence in the household also has an impact on AAM. While the presence of brothers or step-brothers decreases the AAM, the absence of a father or father figure

decreases it[18,26]. This phenomenon has been attributed to the 'paternal investment' theory, which theorises that within the first few years of life, young females perceive and assimilate information regarding paternal investment. This information is used to set and regulate neurophysiological systems involved in puberty and menarche, and also makes selected sexual behaviours more or less likely in adolescence[26]. Family violence, childhood sexual abuse, and mental health issues are also associated with earlier AAM. There is growing evidence to reinforce the effect of childhood adversity on reproductive lifespan, suggesting that different forms and times of exposure will have differing results in terms of AAM. Prolonged childhood maltreatment causing psychosocial stress may cause chronic elevation of the hypothalamic-pituitary- adrenal/gonadal axis and thus expedite AAM [1,23].

1.3.3 Delayed menarche

Despite the above, it is also plausible that poverty and neglect associated with nutritional deprivation may be associated with delayed menarche through suppression of the HPA/G axis [1,18]. There has been some overlap noted between the stressors causing early and late menarche; however in general prolonged exposure to problems such as war conditions, verbal and excessive physical abuse, maternal alcohol abuse, and conflict within the home are associated with delayed AAM [1,18] Several studies have shown that multiple pregnancies may also be a risk factor for delayed menarche[16,17]. Breastfeeding has also been found to be associated with delayed menarche. One mechanism proposed for this is that formula fed infants, when compared to breastfed infants have higher body fat levels, which may explain why formula fed girls attain menarche relatively earlier[19]. The role of EDC in

delayed menarche is still under scrutiny but it is thought that atrazine, a herbicide, delays pubertal development in both sexes by the reduction of LH and prolactin[18]. Generally menarche also occurs later in athletes. Theories to explain this include lowered body fat composition and a negative feedback effect on the hypothalamus exerted by intense exercise [18].

Recently, an association between type 1 diabetes mellitus and delayed menarche has also been proposed. Researchers have observed that the delay in menarche is in direct proportion to the duration of disease, and glycaemic control[27,28].

1.4 BIRTHWEIGHT, CHILDHOOD GROWTH AND MENARCHE

Prenatal life is one of the most important and dynamic phases in human growth. During this time there are periods during which developing tissues may be particularly vulnerable to environmental influences. As previously discussed, interference during this crucial time can lead to chronic disease with associated morbidity and mortality. Because of the inherent difficulties in measuring the intrauterine climate and changes in fetal growth, surrogate markers must be employed. Birth weight is one surrogate of fetal growth which can be used to infer the adequacy of growth and intrauterine milieu[29].

Numerous studies have elucidated the association between low birthweight (LBW) and early AAM, particularly when followed by rapid weight gain in infancy[30,31,32,33,34,35,36,37]. Adair found that despite the fact that birthweight was not statistically significantly related to AAM, girls who were short and light had a delay of menarche of approximately 6 months when compared to those that were tall and thin at birth (see figure 3). Additionally, it was found that this difference was exaggerated in those with above average growth in the first 6 months of life. She therefore postulated that fetal programming in utero has a lasting effect on later growth and maturation, and that these effects are amplified by rapid growth in the postnatal period[32].

Terry et al found that for every unit increase in birthweight, menarche was delayed by 0.34 years. The same study found early weight gain from 4 months to 1 year and 1 year to 7 years to be associated with earlier menarche, with every unit weight gained associated with an 8% and 6% decrease in the age of menarche respectively[36]. Ruder et al (2010) found

that birthweight was inversely associated with menarche, (for each 500g increase in birthweight menarche was delayed 0.21 years) this association, as well as the effect of growth from 0-2 years is dissipated via the mediating effect of later childhood growth[37].

This association holds true for children born small for gestational age (SGA), which on its own has been linked to metabolic and endocrine disorders, as well as short stature, obesity, cardiovascular disease, and diabetes[38]. Menarche is also thought to be influenced by gestational age, with prematurity being an independent risk factor for early AAM[39,40].

Contrasting research in which birth weight was found to be inversely proportional to AAM has been published[41,42]. Zhang et al assessed the effect of birthweight on menarche using the National health and Nutrition Examination Survey (NHANES 2003-2006). They found that although lower birthweight babies showed earlier AAM, their analysis also showed an earlier attainment of menarche in high birthweight babies. They suggested that birthweights at either end of the spectrum may be associated with earlier AAM, and that of these higher birthweight may be the more prominent variable[41]. Similarly, Wang et al illustrated earlier menarche in girls with higher birthweights[42].

Rapid postnatal growth in infancy, or 'catch-up' growth is a well-established phenomenon, often encouraged by health care practitioners. Studies are now demonstrating that this may not in fact be beneficial and may be associated with a number of adverse effects including increasing risk for chronic disease in later life[43]. Regardless of the effect that birthweight is purported to play, the majority of studies found that rapid postnatal growth was associated with

earlier menarche [34,37,41,42]. Research by Wang et al showed that higher birth weight is associated with earlier menarche, and that for every unit increase in weight in the 2-5 year age group, a decrease of 0.05 in the mean log age at menarche could be expected[42]. Although showing contrasting results in terms of birthweight to the above study, Ong et al also showed a strong correlation between weight gain in infancy and early menarche. Their results demonstrated that for every unit of weight gain SD score between birth and 9 months, menarche was decreased by 34%[44]. Notably, the majority of this research has come from the developed world, although one paper from the Philippines was reviewed, where the findings may be more comparable to the South African population in terms of sociodemographic characteristics[43]. Notably this study indicated no influence of birthweight on menarche, except when birth length was also considered. The findings also indicated a strong correlation between faster growth rates in early infancy

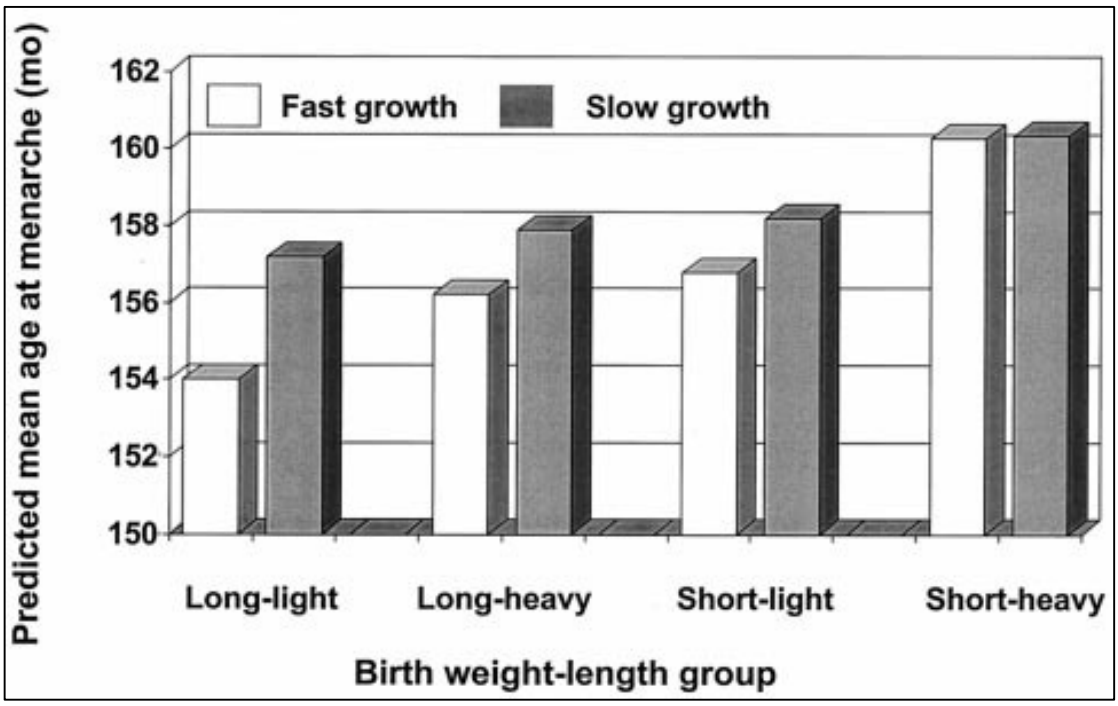


Figure 3 Relationship between birthweight, childhood growth, and menarche, taken from Adair, LS34[32]

Childhood growth patterns are thought to have an impact on many adult characteristics such as puberty, and many comorbid diseases i.e. CVD and type 2 diabetes. It is yet to be demonstrated whether poor fetal growth, poor or rapid infant growth, early or late puberty, or which combination of these exposures is more deleterious in terms of later adult outcomes[45,46]. Maximum discrepancies in rates of weight gain are seen in the first two years of life during the phase of catch up or catch down growth. These variable growth rates are seen usually in response to prenatal growth restriction or macrosomia and are usually complete within the first 18 months of life as the genetically imprinted growth point is reached and the child begins to grow along its genotypically predetermined pathway [47,48]. Because of the possible long term deleterious effects of weight gain in infancy and childhood it is

valuable to researchers to determine and evaluate these specific periods of weight gain in infancy and childhood.

Mechanisms by which both birthweight and childhood weight gain affect menarche are likely to be multifactorial, but several theories have been suggested. One proposal is that antenatally the neuro-endocrine axis is programmed during the so-called 'critical phases' of development (as discussed in the Barker Hypothesis above). This programming may or may not be modified by intra-uterine growth restriction, and leads to imprinting of the fetal hypothalamic-pituitary-gonadal (HPG) axis which is subsequently modified by additional fat acquisition during childhood[31,33].

A second mechanism whereby birthweight childhood weight gain may affect AAM is through the development of hyperinsulinaemia and insulin resistance. Various studies have shown that intrauterine growth restriction, especially during catch up growth is related to the development of impaired glucose intolerance and hyperinsulinaemia[48,49]. Veening *et al* found that SGA children showed a reduced sensitivity to insulin, particularly when this smaller birth weight was compensated for by early catch up growth in infancy[48]. Soto *et al* in 2003 found similar results in that SGA infants at one year showed significantly higher fasting insulin levels and tended towards higher triglycerides[49].

Researchers believe that childhood insulin insensitivity in SGA children may increase risk of developing NIDDM in adult life. This risk is further heightened in those SGA children with catch up growth in childhood and high BMI[48].

The underlying processes behind this model are not fully understood, but there is a relationship between early puberty, hyperinsulinaemia, and

hyperandrogenaemia[50,51]. Girls with premature pubarche show impaired glucose tolerance levels on oral glucose tolerance testing (OGTT), both before and after puberty. They also show signs of insulin resistance and hyperinsulinaemia persisting throughout puberty. This is evidenced by decreased levels of sex hormone binding globulin (SHBG), insulin- like growth factor binding protein-1 (IGFBP-1) and high density lipoprotein (HDL), with corresponding raised levels of triglycerides, very low density lipoproteins (VLDL) and total cholesterol [51].

1.5 THE SIGNIFICANCE OF MENARCHE

The study of menarche and the factors affecting it is significant for various reasons.

Menarcheal age is a widely used measure of sexual maturation, therefore it can be used as a yardstick to gauge the growth, development and ability to reproduce not only of individuals, but also of populations as a whole. Thus researchers are able to monitor aspects of female health through the changes in menarcheal age. One example of this is the study of the secular trend in the age of menarche over time, and being able to make important observations regarding puberty, menarche and female health.

The study of problems relating to adolescent and reproductive health is of importance as they affect both the adolescent and future generations[52].

Menarche is also culturally significant. In many cultures it represents entry into womanhood, is one of the more tangible indicators of a girl's transition into womanhood, and in some cultures coincides with sexual activity[52,53].

The study of menarche is equally relevant because the age at which it occurs has implications for the individual in later life.

Early menarche has been associated with a higher body mass index (BMI). This, and the associated metabolic syndrome (a group of disorders including obesity, hypertension, hypercholesterolaemia/dyslipidaemia and insulin resistance) have been linked to the more dire consequences of Type 2 diabetes and coronary vascular disease[18,54,55]. While the mechanism for the above association remains unclear, the knowledge of menarcheal age may

aid in identification of those at risk of morbidity and mortality from chronic disease later in life.

Numerous studies have also confirmed the link between early menarche and breast cancer. This may be as a consequence of earlier onset of menstruation and therefore earlier exposure to the accompanying hormonal milieu[17]. Others postulate that earlier menarche is also linked to central obesity, and as a result is associated with increased levels of insulin, insulin-like growth factor, and testosterone, which causes mammary proliferation and may foster mammary carcinogenesis[18]. Other cancers, such as ovarian carcinoma, have also been related to AAM, with the risk of ovarian cancer inversely proportional to the age, and decreasing by 9% for every year that menarche is delayed over 12 years of age[9,56]. Seropositive rheumatoid arthritis has also been found to be a consequence of early AAM, and can cause significant morbidity in later years[57].

Additionally, early menarche has been linked to a number of psychosocial disorders, such as early sexual intercourse, depression, delinquency, eating disorders, and poor performance at school [1,25,26]

In a 37 year follow up of over 61 000 women conducted in Norway, published in 2007, all-cause mortality was found to be significantly higher in those with very early or significantly later menarche[58]. Delayed menarche is also been implicated as a risk factor for multiple other comorbidities such as depression, low bone mineral density, and fractures [1]. In terms of bone health, AAM has been linked not only to bone mineral density, but bone microstructure, and girls with delayed menarche are at increased risk of fractures and osteoporosis. This is thought to be as a result of a shorter duration of

exposure to the protective effects of oestrogen, but a genetic component may also play a role[18]. Emerging evidence shows an association between delayed AAM and irregular menses with a particular focus on its role in subfertility[27,28]

1.6 GAPS IN EXISTING KNOWLEDGE

While information exists regarding this topic, the majority of data is available mostly from international sources and developed countries, and little data exists on this topic from low/middle income countries, and almost none drawn from South African populations. Our study will therefore be able to provide a unique local perspective to this global question.

Research has also yet to ascertain the relative impact of prenatal versus childhood environmental and lifestyle factors with regards to menarche.

There is a paucity of data with regards to early childhood weight gain. In many prospective studies investigating the role of childhood weight and menarche. This leads to difficulty differentiating which specific periods of the early childhood years makes the most significant contribution to the overall effect on AAM, If childhood growth has critical windows in terms of its effect on the timing of menarche, those periods can then be the focus of intervention. This is also particularly relevant in a developing country such as South Africa, where the fairly high rates of LBW babies and childhood malnutrition may be having a significant effect on pubertal development.

2 PROBLEM STATEMENT AND HYPOTHESIS

Our study was designed to identify the average age of menarche and critical anthropometry in South Africa, and investigate whether birthweight and childhood growth has an influence on the age at menarche, using representative South African data from the Birth to Twenty cohort.

Based on previous results, our hypothesis is that lower birth weight babies will experience earlier menarche.

3 OBJECTIVES

Using data from the Bt20 prospective cohort the objectives of our study were:

1. To describe the age of onset of menarche in a population of healthy 'normal weight' females in the Birth to Twenty cohort.
2. To demonstrate the influence of birthweight on the average age of menarche
3. To assess the impact of infant and childhood growth on the average age of menarche.
4. To evaluate which growth period has the maximal effect on age at menarche

4 SUBJECTS AND METHODS

4.1 STUDY POPULATION AND SETTING

The Birth to Twenty (BT20) cohort began in 1990 when approximately 3273 mothers with singleton pregnancies who, in addition planned on continued residence within the Soweto-Johannesburg area for six months post-delivery, were recruited from April to June of that year. Richter et al have published a detailed cohort profile illustrating the study sample, objectives, and attrition, but for the purposes of this study a short summary will suffice[59].

The BT20 study includes all singleton children born to women in Soweto-Johannesburg area during proscribed 7-week enrolment interval. The original study was designed to investigate participants in terms of a broad spectrum of attributes including health and educational development.

Due to the fact that the sample for the cohort was drawn from the Soweto-Johannesburg area, which in itself is one of the most densely populated black metropolitan residential regions in South Africa, black children made up the majority of the sample at 78,5%. Coloured children comprised 11% of the sample, followed by white (6%) and Indian (3.5%) children[59].

Thus it can be seen that while the sample may be demographically representative of the resident families in the Soweto-Johannesburg area, it cannot be said to be wholly representative of a homogenous South African population. This is in part due to the area from which recruitment occurred (as defined above). It is also supposed that during the time frame in which recruitment took place, white families relied heavily on private sector health facilities from which recruitment did not take place. In addition to this, attrition rates in white families were found to be higher as the study progressed,

adding to the smaller sample size[59].

4.2 EXPOSURES: INFANT AND CHILD ANTHROPOMETRIC MEASURES

Gestational age was based on the mothers last menstrual period and infant birth date.

Birthweight was measured at birth using hospital scales. LBW is defined as a weight 2500g or less as proscribed by the World Health Organisation[60]

4.3 OUTCOME VARIABLES

Age at menarche, the main outcome of interest, was based on reported age by participants.

4.4 POTENTIAL CONFOUNDERS

Potential confounders include maternal factors such as maternal age, parity, marital status, SES and maternal education. For the purposes of this study wealth quintiles are used to convey maternal SES, with 0 denoting no income, and 5 denoting the opposite extreme of wealth. Maternal education has been divided into three levels with 0 symbolising education up to primary school level, 1 denoting secondary school education, 2 up to high school, and 3 representing tertiary education.

4.5 ANALYTIC SAMPLE

The Bt20 cohort consists of a sample size of 3273. Of those, males were excluded, leaving 1682 participants. Once those females who had incomplete data for the study variables were excluded, our analytic sample consisted of 788 participants.

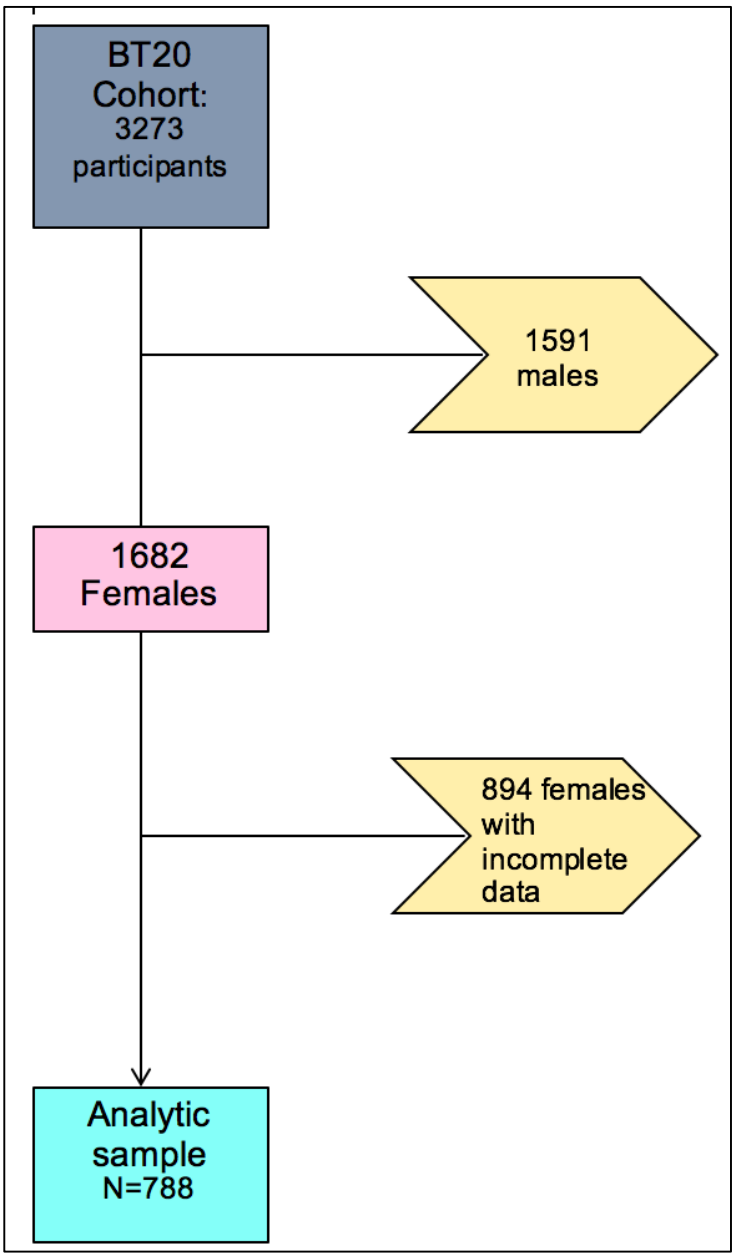


Figure 4 Diagram showing analytical sample distribution

4.6 DATA MANAGEMENT AND STATISTICAL METHODS

Analysis was conducted using Stata statistical software package. Descriptive statistics were calculated including means ± SD, proportions, medians with ranges and frequencies with percentages. The association between age at menarche and birthweight, growth, and maternal variables was evaluated using χ^2 and *t* tests, with menarche dichotomised as either earlier (< 12.5

years) or normal (≥ 12.5 years). Bivariate correlations between two variables were examined. We then used linear regression models to quantify the association between each proposed exposure and the outcome (AAM). Logistic regression was utilised to calculate odds ratios and assess the risk of early menarche in the face of certain exposures and proposed confounders.

Because of the statistical difficulties associated with modelling strongly correlated weight measurements, conditional weight (CW) variables were calculated. Conditional weight variables at each given age were used to represent that constituent of the weight that is not correlated with preceding weight measurements. CW's were calculated as the residuals from linear regressions of weight (at specific ages) on birth-weight, and prior weights. Therefore at its core a CW will represent the deviation on an individuals' growth from an expected value that is calculated using his/her prior weights. Using a conditional weight variable in a multiple regression with the variables it is conditioned on allowed us to then view each variable as a change in weight over the preceding interval.

4.7 ETHICS

Patient confidentiality was maintained throughout the study. Ethical clearance was acquired for the original study from the medical Human Research Ethics Committee for the University of the Witwatersrand protocol number 24/1/90 (appendix A). Further ethics approval to carry out this secondary study was given (see appendix B).

5 RESULTS

5.1 THE ANALYTIC SAMPLE

Table 1 Comparison between the analytic sample and the cohort

Variable	Analytic sample		Cohort		*P* Value	χ2 value
	No.	Value	No.	Value		
Infant and early life						
Gestation at delivery (weeks)	788	38.02 (1.98)	838	38.24 (1.90)	0.0226	
Birthweight (kg)	788	3.03 (0.50)	892	3.01(0.50)	0.5721	
Birthweight z-score	788	-0.51 (1.18)	892	-0.55 (1.17)	0.5795	
Weight at 24 months (Kg)	788	11.21 (1.40)	337	11.26 (1.30)	0.5611	
Weight at 24 months conditional ((kg)	788	-0.01 (1.02)	316	0.03 (0.94)	0.5294	
Weight at 48 months (kg)	788	15.26 (2.05)	350	15.42 (1.89)	0.2322	
Conditional weight at 48 months (kg)	788	-0.02 (1.06)	289	0.05 (0.80)	0.2962	
Menarche	788	12.66 (1.20)	318	12.69 (1.30)	0.7145	
Maternal statistics						
Maternal Age	788	25.59 (6.20)	892	26.21 (5.98)	0.0365	
Parity						
One child	322	51.11	308	48.89	0.007	7.3484
Two or more children	466	44.30	586	55.70		
Level of education						
Primary school education	5	18.52	22	81.48	0.000	130.1646
Secondary school education	618	56.08	484	43.92.		
Tertiary education	78	22.35	271	77.65		
Marital status						
Married	273	38.18	442	61.82	0.000	40.70
Unmarried	515	53.93	440	46.07		
Socioeconomic status						
1	61	62.24	37	38.00	0.091	8.02
2	80	59.30	55	41.00		
3	149	57.31	111	43.00		
4	85	53.00	76	47.20		
5	62	46.30	72	54.00		

The analytic sample consists of the participants who met all the inclusion criteria. The cohort sample incudes all the subjects in the BT20 cohort regardless of whether the data for each subject was complete or not. The analytic sample consists of 788 participants, with the size of the remainder of the cohort ranging from 289 to 892, depending on the variable in question. Level of education, marital status, and socioeconomic status are confounding variables that were not part of the selection criteria, therefore the size of the sample with respect to those variables is 701, 788, and 437 respectively. The two samples are very similar in terms of early and infant life statistics. In terms of maternal statistics, there was a non-significant difference found between the two study groups when looking at levels of education, marital status and socioeconomic status.

Table 2 Summary statistics

Variable	No.	Value
Infant and early life		
Gestation at delivery (weeks)	788	38.02
Birthweight (kg)	788	3.03
Birthweight z-score	788	-0.51
Weight at 24 months (Kg)	788	11.21
Weight at 24 months conditional (Kg)	788	-0.012
Weight at 24 moths z-score (Kg)	788	-0.34
Weight at 48 months (kg)	788	15.26
Conditional weight at 48 months (kg)	788	-0.19
Weight at 48 months z-score (Kg)	788	-0.45
Menarche	788	12.66
Maternal statistics		
Maternal Age	788	25.56
Parity		
One child	322	51.11
Two or more children	466	44.30
Level of education		
Primary school	5	18.52
Secondary school	618	65.10
Tertiary education	78	22.40
Marital status		
Married	273	38.20
Unmarried	515	54.00
Socioeconomic status		
1	61	62.24
2	80	59.30
3	149	57.31
4	85	53.00
5	62	46.27

Infant and early life statistics: The average gestation at delivery was 38.02 weeks. Birthweight for the sample was 3.02kg. Average weight at 24 months 11.21kg, with a conditional weight of -0.012kg. Weight at 48 months was on average 15.26kg, with a conditional weight of -0.19kg.

Maternal statistics:

The maternal age was on average 25.56 years.

The following categorical variables were expressed as n(%)

Of a sample size of 788, 51.11% of mothers had one child, 44.30% had more than one child. 18.52% of mothers had only a primary school education, 65.10% had a secondary school education, and 22.40% had the opportunity for tertiary education. Unmarried mothers were in the majority making up 54% of the sample, while 38.2% were married. 62.24% of mothers belong in the lowest category of SES, while 46.27% in the highest.

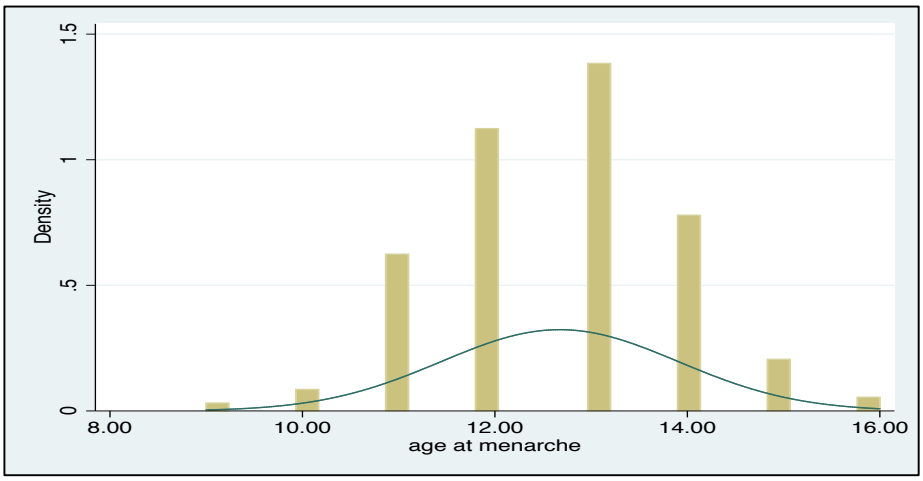


Figure 5 Normal distribution of menarche in the Birth to Twenty cohort, with an average age of 12.7 years.

Figure 5 is a graph showing the normal distribution of menarche in the study population. The range of AAM was found to be 9 years, to 16 years, with an average of 12.7 years.

5.2 CORRELATIONS

Table 3 Correlation matrix showing the significance of correlations between AAM and birthweight, gestational age and childhood weight gain in the Birth to Twenty cohort

	Birthweight	Gestational age	Weight at 24 months	Conditional weight 24 months	Weight at 48 months	Conditional weight 48 months
Birthweight	1.00					
Gestational age	0.52*	1.00				
P-value	0.00					
Weight at 24 months	0.33*	0.10*	1.00			
P-value	0.00	0.0115				
Conditional weight 24 months	0.01	-0.06	0.92*	1.00		
P-value	0.72	0.10	0.00			
Weight at 48 months	0.34*	0.14	0.75*	0.65*	1.00	
P-value	0.00	0.00	0.00	0.00		
Conditional weight 48 months	0.00	0.03	-0.01	-0.04	0.60*	1.00
P-value	0.95	0.48	0.85	0.32	0.00	
Age at menarche	0.01	0.00	-0.18*	-0.20*	-0.21*	-0.11*
P-value	0.88	0.96	0.00	0.00	0.00	0.00
Maternal age	0.0619	0.06	0.06	0.05	0.06	-0.01
P-value	0,08	0.11	0.08	0.16	0.09	0.73

Statistical significance in this matrix is denoted by an asterisk. There is a very weak correlation between AAM and birthweight that is not statistically significant. No correlation between gestational age and birthweight was found. There is a weak but statistically significant correlation between weight at 24 months and AAM (for every unit increase in weight there is a 0.18-year decrease in AAM. It is also weakly correlated to the conditional weight at 24 months- for every unit increase in weight there is a corresponding 0.21-year decrease in AAM. Weight at 48 months and conditional weight have a similar weak but statistically significant correlation to AAM. For every unit increase in eight at 48 months and conditional weight at 48 months there is a decrease in 0.21 and 0.11 years of menarche respectively.

5.3 LINEAR AND LOGISTIC REGRESSION

Table 4 Linear regression of maternal, neonatal, infant, and childhood variables on menarche in the Birth to Twenty cohort

Variable	Model 1		Model 2		Model 3		Model 4		Model 5	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Neonatal and infant statistics										
Birthweight (Z-score)	-0.00	-0.07, 0.07					-0.00	-0.07, 0.07	-0.01	-0,10, 0,08
Conditional weight 24 months (kg)			-0.23	-0.31, -0.15			-0.24	-0.32, -0.16	-0.21	-0.30, -0.12
Conditional weight 48 months (kg)					-0.13	-021,-0.05	-0.14	-0.21, -0,06	-0.16	-0.24, -0.08
Gestational age (months)									-0.14	-0.70, 0.04
Maternal statistics										
Maternal age (years)									-0.01	-0.26, 0.01
Parity									0.25	0.02, 0.47
Maternal education										
Primary school										
Secondary school									-0.12	-1.17, 0.92
Tertiary education									-0.09	-1.18, 0.99
Marital status									-0.08	-0.30, 0.13
Socioeconomic status										
2									-0.16	-0.51,-0.18
3									-0.15	-0.50,0.10
4									-0.30	-0.60,0.60
5									-0.40	-0.75,'-0.10
r squared value	0.0000		0.0371		0.0116		0.0492		0.0723	

From model 1 it can be seen that there is no correlation between birthweight

and AAM. Model 2 shows that a weak correlation exists between conditional weight at 24 months and AAM which is statistically significant. The r^2 value is 0.0371, meaning that 3.7% of the variance in AAM can be explained by weight at 24 months alone. Model 3 illustrates a further weak but significant correlation between conditional weight at 48 months and AAM, with the r^2 value showing that 1.1% of the variation in menarche can be attributed to weight at 48 months. Model 4 again shows no correlation between birthweight and small but significant correlations between conditional weights at 24 and 48 months when regressed on AAM together. The r^2 value indicates that together these exposures are accountable for 4.9% of the variation in AAM noted. When all exposures are regressed together on AAM, Model 5 shows that birthweight, gestational age, maternal age all show weak and non-significant correlations to AAM. As expected conditional weights at 24 and 48 months show a weak but significant correlation to AAM. Parity is significantly but weakly correlated to AAM, with every unit increase in parity associated with a 0.25 year decrease in AAM. In terms of maternal education, having an education up to primary school level is not significantly associated with AAM, but having secondary or tertiary education is, with a 0.09 year and 0.08 year decrease in menarche for every unit increase in education respectively. The extremes of wealth seem to be influenced by menarche with the lowest and highest levels of wealth associated with a weak but significant decrease in the AAM. Levels of wealth between the extremes had no significant correlation to AAM. The r^2 value for this model indicated that all exposures together account for 7.2% variation in AAM.

Table 5 Logistic regression of variables on early menarche

Variable	Odds ratio	95% CI
Neonatal and infant statistics		
Birthweight (Z-score)	0.99	0.84, 1.16
Conditional weight 24 months (kg)	1.42	1.21, 1.67
Conditional weight 48 months (kg)	1.18	1.02, 1.37
Gestational age (months)	1.01	0.91, 1.11
Maternal statistics		
Maternal age (years)	1.03	1.00, 1.07
Parity		
One child	1 (reference)	
2 or more children	0.72	0.49, 1,06
Maternal education		
Primary school	1 (reference)	
Secondary school	2.47	0.30, 23.21
Tertiary Education	3.03	0.31, 30,12
Marital status		
Unmarried	1 (reference)	
Married	1.10	0.73, 1,54
Socioeconomic status		
1	1 (reference)	
2	1.14	0.62, 2.10
3	1.10	0.64, 1.90
4	1.31	0.73, 2.34
5	1.43	0.77, 2,63

5.3.1 Neonatal and infant statistics:

The birthweight z-score and gestational age had odds ratios of near 1, denoting that those exposures have no effect on early menarche. Both conditional weights at 24 months and 48 months had odds ratios of above 1, which are statistically significant. This implies that those variables are associated with higher odds of early menarche in a proportional relationship. Conditional weight at 24 months is shown to increase the odds of early menarche by 42%, while conditional weight at 48 months the odds of early menarche are increased by 18%.

5.3.2 Maternal statistics:

Table 5 shows that maternal age had an odds ratio of 1, therefore it is not likely to have an effect on early menarche. Having two or more children decreases the likelihood of early menarche by 0.72 times but this is not statistically significant. Secondary and tertiary school education in those model has been found to be associated with early menarche with secondary and tertiary school increasing the odds of early menarche by 2.47 and 3.03 times which is also not statistically significant. Married and unmarried mothers have essentially equal odds ratios of 1 which infers that they have no effect on early menarche. All quintiles of socio-economic status have some effect on early menarche, none of which have been found to be significant.

6 DISCUSSION

6.1 AGE AT MENARCHE

The average age of menarche in our sample was 12.66 years. This is slightly higher than the previous ages estimated in the South African study by Jones et al in 2009. This may be accounted for by the smaller analytical sample in the previous study.

These findings are similar to other international studies that also reported earlier menarche in babies who had weight gain in infancy[34,36,42]. Tam et al illustrated a mean AAM of exactly 16.6 years. The data for that study comes out of Penrith, Australia, and differs from our study in that more than 96% of the participants were white or of European descent [34]. The mean age of the overall cohort in a study by Terry et al[36] was 12.5 years. The data from that study comes from the National Collaborative Perinatal Project and details women born in New York in the United states from 1959 to 1963 (this study had white, black and Puerto Rican women in roughly equal thirds).

Wang et al[42], using data from the North Carolina Infant Feeding Study (predominantly white, well educated families) reported a mean age of 11.7 in black girls, and 12.7 in white girls.

One can infer from this that Despite the differences in ethnicity, socioeconomic circumstances, and the age of the study, the average age of menarche across these studies is remarkably similar.

6.2 BIRTHWEIGHT AND MENARCHE

One of the main objectives of this study was to investigate the relationship between birthweight, and age at menarche. The association between low birthweight (LBW) and early AAM, particularly when followed by rapid infant weight gain has been illustrated by a number of studies [30,31,33,35]. Romundstad et al[30] found that early age at menarche was associated with lower birthweights. Cooper et al[31] also found that girls who reached menarche earliest had low birth weights at delivery. Additionally, Tam et al[34] illustrated that girls born long and light achieved menarche roughly six months before their long/heavy and short/light counterparts, and a year before those girls born short and heavy.

Contrary to the above findings and our hypothesis, the findings of this study show that birthweight does not significantly affect AAM. This may be explained by the fact that this study did not take birth length into consideration. One study supporting this theory is that of Adair[32] who in fact found no association between birthweight and menarche except when birth length was taken into account.

6.3 CHILDHOOD GROWTH AND MENARCHE

Adair[32] and numerous other authors have found that faster growth rates in early infancy are a significant predictor of earlier age at menarche [34,37,41,42]. Wang et al showed a decrease of 0.05 in the average log age at which menarche could be expected with every unit increase in weight in the 2-5 year age group [42]. Ong et al showed a strong correlation between weight gain in infancy and early menarche demonstrating that for every unit of weight gain SD score between birth and 9 months, menarche was decreased by 34%. In

their study of 2715 girls from a prospective United Kingdom birth cohort study, the above researchers also found that rapid weight gain specifically from birth to 2 months and 2-9 months correlated with earlier age at menarche in girls[44].

Our analysis does however, show a sustained and significant relationship between AAM and weight at 2 years, and weight at 4 years of age, with growth in the first 24 months having the greatest effect.

6.4 LIMITATIONS

Exclusion of above 50% of our original sample size due to missing data represents one of the major limitations of this study.

A lack of birth length data and conditional weights independent of length are another limitation. This would help to distinguish those girls born appropriately small for gestational age and those with intrauterine growth restriction, and may help tease out some of the nuances around the use of birthweight as a marker for intrauterine health.

In terms of looking at menarche in South Africa, it may also be useful in future studies to subdivide the participants into race groups in order to obtain more specific data. Given that menarche is controlled in part by genetics and race, one is limited when all groups are bracketed under one mean.

Future research may want to focus on the relationship between weight, length, and AAM. In this analysis we were unable to distinguish between those babies born SGA due to IUGR and those those constitutionally small babies. This may be an important distinction if testing the fetal programming hypothesis is a primary aim. Additionally, it would be helpful to include antenatal maternal information such as skinfold thickness, BMI, dietary

information into further studies to contribute to a better understanding of the fetal programming hypothesis and birthweight as a possible marker of intrauterine life.

It would also be interesting for prospective studies to look at adult outcomes of these participants in terms of obesity, metabolic, and cardiovascular disease, and get an appreciation as to whether the fetal origins hypothesis is holding true for obesity, menarche and related diseases. This research could also be applied to males, and further research could look towards whether the above relationships between weight gain and timing of puberty in females are applicable to males.

6.5 STRENGTHS

Strengths of the study include a large sample size and the longitudinal nature of the cohort, allowing for a better insight into childhood growth. It is also a representative sample of the urban South African environment, which makes it relevant to our setting and applicable in other low-middle income countries.

This study has implications on many levels across numerous disciplines. South Africa is a developing country. It has correspondingly high rates of preterm labour, intra uterine growth restriction, LWB, poor childhood nutrition, and increasing rates of childhood and adult obesity levels, as well as high of teen pregnancy rates. These factors are of increasing relevance as exposures for early AAM. Obesity is an exposure for early menarche as well early menarche being a risk factor for adult obesity. Early menarche is a risk factor for teen pregnancy. It can be seen from the above that knowledge on the long term impact of childhood growth is important. If one is to have a positive impact on the above problems, clearly there must be an undertaking to

understand the underlying mechanisms, but in the interim interventions must be put into place to avoid long term detrimental effects.

7 CONCLUSION

In conclusion, faster weight gain in infancy during the first 24 and 48 months is associated with earlier AAM in girls. This has major implications for clinical practice especially in developing countries. The underlying mechanisms are very poorly understood, and more research in this area is required to understand the elaborate environmental and genetic interactions underpinning the effect of the antenatal environment, childhood growth, and menarche.

8 APPENDICES:

8.1 APPENDIX A: ORIGINAL ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

DOCUMENT A79/55

COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS
(REF. R14/49)

CLEARANCE CERTIFICATE

PROTOCOL NO: 24/1/90

PROJECT : BIRTH-TO-TEN STUDY
(OVERALL PROTOCOL)

INVESTIGATOR/S : DR S FONN

DEPARTMENT : ANATOMY, MEDICAL SCHOOL

DATE CONSIDERED 19 JANUARY 1990

RECOMMENDATION OF COMMITTEE :

APPROVED [X] subject to:

Progress report required after one year.

Date : 24/1/90 CHAIRMAN : .....
Professor P E Cleaton-Jones

Guidelines for written "Informed Consent" attached where applicable.

DECLARATION BY INVESTIGATOR/S
To be completed in duplicate and ONE copy returned to Miss S M Boshoff,
Office of the Deputy Registrar (Research), Room 10002, 10th Floor,
Senate House, University.

I/we fully understand the conditions under which I am/we are authorised to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions.

Should any departure be contemplated from the research procedure as approved I/we undertake to resubmit the Protocol to the Committee.

DATE : SIGNED :

8.2 APPENDIX B: ETHICS CLEARANCE FOR THIS STUDY

R14/49 Dr Frances Paterson

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M141131

NAME: (Principal Investigator)	Dr Frances Paterson
DEPARTMENT:	Obstetrics and Gynaecology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Birthweight, Childhood Growth and Menarche in South Africa
DATE CONSIDERED:	28/11/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr KA Frank
APPROVED BY:	Professor Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	01/12/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

8.3 APPENDIX C: TURNITIN REPORT



Turnitin Originality Report
literaturereviewref.docx by Frances Paterson
From MMED Turnitin
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Handbook of Growth and Growth Monitoring in Health and Disease, 2012.

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