Female Pubertal Development in the United Kingdom: Trends in Onset, Progress and Duration from 1948 to the Present

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Abstract

Female pubertal development is the process of physical changes from the child to adult female bodies. The nature of human adaptation creates huge inter and intra-population variation in female pubertal development in response to both heritable and environmental determinants.

Age at menarche has been declining globally in response to urbanisation and industrialisation. In the USA and other developed countries age at pubertal onset, specifically age at thelarche, appears to be declining with the concurrent rise in overweight and obesity.

Longitudinal cohort datasets from the UK were analysed to replicate these findings in the UK population from 1948-2005. These data show evidence for a continued downward secular trend in age at menarche, and show a downward secular trend in age at pubertal onset, in response to increased weight status. Over the period 1948-2005, age at menarche decreased by 0.30 years, and age at thelarche decreased by one year. The average interval between pubertal onset and age at menarche increased from 2.3 years to 2.7 years. More than half of the total decrease in age at thelarche took place between 1980 and 2001.

Some of the variance in pubertal development, and specifically the large decrease in age at thelarche, may to be the result of increasing exposure to endocrine disrupting chemicals over the last 50-60 years. Lipophilic endocrine disruptors have the potential to accelerate pubertal development in overweight girls who have the capacity to store dangerous levels of these toxic substances in their high fat mass.

The changes in timing and tempo of female pubertal development in the UK should be considered on a continuum of adaptive plasticity that is evident in the population variation of female pubertal development, rather than measuring recent changes as pathology.

Earlier age at puberty has a number of implications for negative health outcomes, specifically increased risk of reproductive cancers. Moreover, the interaction between increased weight status and increased exposure to endocrine disruptors may exacerbate these negative effects.

Preface

Introduction:

This thesis considers the factors affecting age at female pubertal onset and the process of pubertal development. More specifically, the purpose of this thesis is to consider and explain changing age at puberty among girls in the UK over the last 60 years by examining whether there is a trend for earlier age at onset of breast development in response to both increased overweight and obesity, and increased exposures to endocrine disrupting chemicals that are capable of mimicking or blocking the actions of endogenous steroid hormones. While focusing on the process of puberty of girls in the UK, this thesis also explores the evident variation in age at puberty among girls who grow up in different populations and ecologies around the globe, in order to build a picture of the degree of plasticity at the onset and during the process of female puberty. This thesis places the changing pubertal schedules of girls in the UK on a continuum of plasticity rather than seeing change as a pathology or deviation from a norm. Changing puberty schedules therefore reflect an evolved response to changing or uncertain ecological conditions.

Aims

The aims of the thesis are as follows:

1) To understand changes in female pubertal development in the UK over the last 60 years and elucidate the possible factors responsible for that change.

2) To consider changing age at puberty and pubertal milestones as an evolved response to shifting ecological and lifestyle conditions.

The Hypotheses I will examine in this thesis are as follows:

1. Given the increase in obesity in the UK in recent years, and an existing association between overweight and earlier age at menarche, age at menarche has continuously decreased in the UK between 1948 and 2005.

Prediction: Data from longitudinal datasets will show a trend for earlier age at menarche across time in the UK.

2. Given the increase in obesity and sedentary behaviours in the UK, which results in long periods of positive energy balance in childhood, age at pubertal onset continuously decreased in the UK from 1948-2005.

Prediction: Data from longitudinal datasets will show a trend for earlier pubertal onset across time in the UK.

3. Decreasing age at thelarche is concomitant with increases in exposure to endocrine disrupting chemicals.

Prediction: Exposure to endocrine disrupting chemicals explains some of the variance in age at thelarche that cannot be explained by increased weight status.

Theoretical framework

To address the aims of this thesis and to specifically test the hypotheses above requires a theoretical framework that provides parameters for understanding and examining changes in pubertal onset. Here I consider the timing of pubertal onset within the framework of Life History Theory (LHT) (See Box 1, p. 3-4). The unique traits that result from those trade-offs established by the apportionment of finite resources in line with LHT characterise the life course and reproductive strategy of a species (see Charnov, 1991 and Stearns 1992). One such trait is age at pubertal onset.

In order to apportion energy to reproductive development and reproductive potential, energetic input into growth and maintenance must be reduced. Moreover, it must be reduced at a point when the energy trade-off would not negatively affect overall health or pose a risk of death. The timing of reproductive onset therefore balances the likelihood of current versus future (or potential) reproductive success given available resources (Charnov, 1991 and Stearns 1992). Moreover, this approach provides a clear framework within which to consider increased energy availability as the result of increased calorie intake and lower activity levels that now characterise girls of pubertal age.

Thesis structure:

In order to meet the overall aims and test the hypotheses set out above, the thesis is structured in two parts: Part I groups the physiological and environmental influences that determine the timing and process of female pubertal development in developed industrialised nations, and developing and subsistence economy populations; in order to introduce a normative biomedical model of puberty by which to measure change, and the response of that model to environmental shifts. Part I then considers to what degree that model is globally representative.

Part II then analyses current understanding of the influence of overweight and obesity on female pubertal development to find evidence of a continued acceleration of pubertal development in the UK over the last sixty years. Part II discusses the evidence for change in female pubertal development in the UK and draws conclusions about the implications of these findings, and whether the model of normal puberty established in Part I remains representative in the UK.

Part I: Environmental influences on variation in the physiology of female pubertal development

Chapter 1: The role of biomedicine in understanding female pubertal development introduces the physiology of pubertal development and considers the clinical understanding of normative models of female pubertal development. This review also introduces and analyses the arguments put forward to explain the mechanisms of pubertal onset and mediating environmental factors that may accelerate or delay puberty. Finally, this Chapter outlines specific methods for measuring puberty in girls, which provides descriptors that will be referred to throughout the rest of the thesis, and reviews the concept of Life History Theory as a framework for understanding the timing of pubertal onset.

Chapter 2: Worldwide variation and ecological influences on female pubertal development first reviews the process and timing of female pubertal development in subsistence populations, where girls are not exposed to obesity or other lifestyle factors associated with urbanisation, in order to demonstrate how this differs from the typical western biomedical model of "normal" puberty; and the roles of lifestyle and ecology on that difference. Chapter 2 second reviews female pubertal onset in populations in transition who are experiencing increasing urbanisation and lifestyle change.

Chapter 3: Endocrine disrupting chemicals and accelerated pubertal development focuses on the role of endocrine disrupting chemicals (EDCs) on female pubertal development. There is growing evidence to suggest that some of these compounds can both influence the timing of pubertal development, and interfere with weight regulation. This Chapter explores the mechanisms by which endocrine disrupting chemicals may be responsible for the recent secular trend in female pubertal onset.

Part II: The changing process of female pubertal development and risks of the modern environment

Chapter 4: The role of overweight and obesity on female pubertal development is a systematic review of literature on puberty and associations with overweight and obesity whereby a reproducible keyword search methodology is applied to search, appraise, and collate relevant literature. This methodology also specifies the sources and time frame of searchable literature. This particular type of literature search methodology was carried out in order to specifically address and collate evidence for a causal relationship between these factors.

A vast majority of the literature concerning changing age at puberty considers overweight and obesity as an important factor in this change. By separating out this specific literature it is possible to collate the results of individual papers in order to determine whether there is strong evidence to support a causal relationship with pubertal acceleration. Moreover, by considering the individual methodologies within the review literature it is also possible to understand how or why this evidence may conflict with literature that point towards very different causal factors. A systematic review also provides a methodology for highlighting those aspects of investigation that require further analyses and may be answered by the application of my chosen methodology in the following chapters in order to meet my thesis aims. As such, this review focuses on human literature only, since no non-human analyses are carried out as part of this thesis.

In this case the sample of literature from the search is too small for a traditional systematic review with a meta-analysis, and instead reproduces the steps of a systematic review by systematically detailing those relationships between overweight and obesity, and female pubertal development that were highlighted from reading the full texts, and detailing what these studies state about those relationships.

Chapter 5: UK trends in age at menarche and age at pubertal onset 1948-2001 describes the collection, content, cleaning, use, and analysis of four longitudinal datasets from the UK in order to find evidence for a change in age at pubertal development over the last 60 years. This Chapter outlines the history of the original studies from which these data were taken and provides a short discussion on the purpose and implications of using longitudinal studies to indicate trends over time. Chapter 5 presents results of these analyses and

reports comparative pubertal measures from each dataset in order to describe the trends in female pubertal development in the UK.

Chapter 6: Plasticity of female pubertal development in response to multiple environmental pressures is a discussion that first explains the implications of the results from the analyses in Chapter 5 by addressing the first aim and the three hypotheses outlined above; and second specifically addresses the second aim of this thesis, which is to place our understanding of the changing process of female pubertal development in the UK on a continuum of evolved plasticity by: 1) drawing together the evidence for a continued secular trend in puberty onset in the UK with evidence for the effects of EDCs on the pubertal process. By considering these two effects together this chapter presents a mechanism to explain changing age at puberty in the UK, which may not be explained by either increased obesity or exposure to EDCs alone; 2) considering the degree of worldwide variation evident in the process of puberty in order to demonstrate the lack of a true "norm"; and 3) drawing on the variation in puberty schedules in various ecologies around the globe to consider change as the result of secular trends as an element of that inherent plasticity. By contextualising change in this manner I consider accelerated pubertal onset – specifically accelerated onset of breast development - not as pathology, but as an evolved response. Finally, this chapter contains a consideration of the implications of accelerated pubertal onset on the health and growth of girls.

The **Conclusion** of the thesis confirms how the original aims were met, and how each section of the thesis contributed to those aims.

PART I

Chapter One: The physiology of female pubertal development

This Chapter provides the physiological background to our understanding of the onset and timing of pubertal development drawn from clinical, auxological and the human biological literature. From recognising variation in the period of maximum height gain, and the resulting tempo of maturation (Boas, 1930; Shuttleworth, 1937), established by the very first longitudinal studies of growth (e.g. Boas, 1897); to recognising the pattern of maturation of the secondary sexual characteristics through repeated measures (Marshall and Tanner, 1969), to recognising population change in maturation in clinics (Herman-Giddens et al., 1997; Parent et al., 2003); these measures have provided the necessary information to determine an "average" maturation schedule. Within that paradigm clinicians and medical researchers have a prescribed view of the typical pubertal process and a range of indicators for normal, healthy maturation versus pathological or abnormal maturation. These indicators, as well as the mechanisms and auxology associated with pubertal onset and pubertal development will be explored in order to determine to what extent this process is changing in response to the modern environment.

Box 1

Puberty

Puberty, from the Latin *pubes*, meaning hair, is the liminal period between the child and adult bodies, which signals the canalisation of childhood development and encompasses all of the physical maturation of the sub-adult in preparation for reproduction. Much of the literature refers to puberty and adolescence interchangeably. Here I consider adolescence to refer to psychosocial and behavioural development, and use the term puberty to refer to the physical changes that take place at and following the re-initiation of the gonadotropin-releasing hormone (GnRH) pulse. This includes: growth in height, changing body shape, the accumulation of fat on the hips and thighs for girls, the appearance of secondary sexual characteristics and the onset of menstruation. While there is some use of the word puberty to refer only to the period of development between regular GnRH pulsing and first menstruation, I define the end of puberty as the completion of both breast development and pubic hair growth.

Thelarche

Onset of breast development. This is the first appearance of the breast bud accompanied by an increase in the area of the areola.

Pubarche

Onset of pubic hair growth. This is marked by the first appearance of sparse hair along the labia.

Menarche

First menstrual bleed.

Pubertal onset

The re-initiation of the GnRH pulse, which is quiescent during childhood, begins a process of neuroendocrine responses that cause the development of secondary sexual characteristics and the maturation of the ovaries and uterus. Here, I use the term specifically to refer to the first outward signs of pubertal development, either via thelarche, pubarche or menarche.

GnRH Pulse

The gonadotropin-releasing hormone (GnRH) pulse. Neuoroendocrine hormone pulse released from the anterior pituitary. GnRH is present during early childhood, quiescent during mid-childhood, and is released at nighttime at pubertal onset in a pulse that increases in frequency to include daytime pulsing as pubertal development progresses. The maturation of the GnRH pulse therefore appears as on-off-on.

Peak Height Velocity (PHV)

Rhe point during growth where velocity is at its greatest. Typically precedes menarche for girls.

Life History Theory (LHT)

This is the theory behind the apportionment of finite energy within the environment to the processes of growth, maintenance, and reproduction; which determine the growth, development and reproductive schedules of an individual. Energy paucity and excess either produces or relieves trade-offs within these central processes, which in turn determine when an individual will invest in current versus future reproduction. In terms of pubertal development LHT apportions energy based on the balance between the necessity to begin maturation versus spending time learning, acquiring skills and growing larger, against the pressures of energy availability, which are variable across different ecologies. (Charnov, 1991; Stearns, 1992)

Puberty is meticulously orchestrated by both the endocrine and central nervous systems (CNS), which promote the development of secondary sexual characteristics and prepare the body for reproduction. Puberty involves a process of changes in neuroendocrine signals, metabolism, body composition, mass, size, and shape in both males and females, which is punctuated by genital growth and maturation. It also includes milestone events like the onset of breast development and menarche in girls, and first nocturnal emission and onset of facial hair growth for boys. It is these differences in maturation that establish the sexual dimorphism evident in adults.

The well-known hallmarks of puberty like the growth spurt and distribution of fat to targeted areas of the body are driven by a battery of hormonal changes. These hormonal changes work both individually and in concert to determine the timing and tempo of the pubertal process. It is likely that the *interactions* between these hormones are as important, if not more so, as their individual targets (Rogol et al., 2002) since such a complex process requires a closely orchestrated sequence or stimuli and responses.

For females, puberty involves the maturation of the uterus, vagina and ovaries and, externally, the development of breasts and pubic hair, as well as feminine traits like shapely hips and thighs (Tanner, 1989). These external traits not only ready the body for the physical demands of reproduction but signal fecundity to males (Cant, 1981; Gallup, 1982; Marlowe, 1998).

Pubertal onset

The onset of pubertal development is not fully understood. The event, or series of events, that prompt the maturation of the reproductive system have yet to be established. However, many of the mechanisms that drive change and growth during pubescence have been elucidated. Adolescence represents the period of quickest growth after infancy. Growth is slow during childhood until adolescence

when there is a quick spurt followed by increasingly slow growth until mature adult stature is reached (Boas, 1932). That quick spurt is known as peak height velocity (PHV), in which the individual has the greatest gain in height per unit of time (Tanner, 1962; 1978). Figure 1.1 shows the typical growth velocity of girls and boys from birth to age 18 years, with PHV occurring around age 12 in girls. For girls PHV tends to occur after the onset of breast development (Rogol et al, 2002) and before first menstruation (Tanner, 1962).

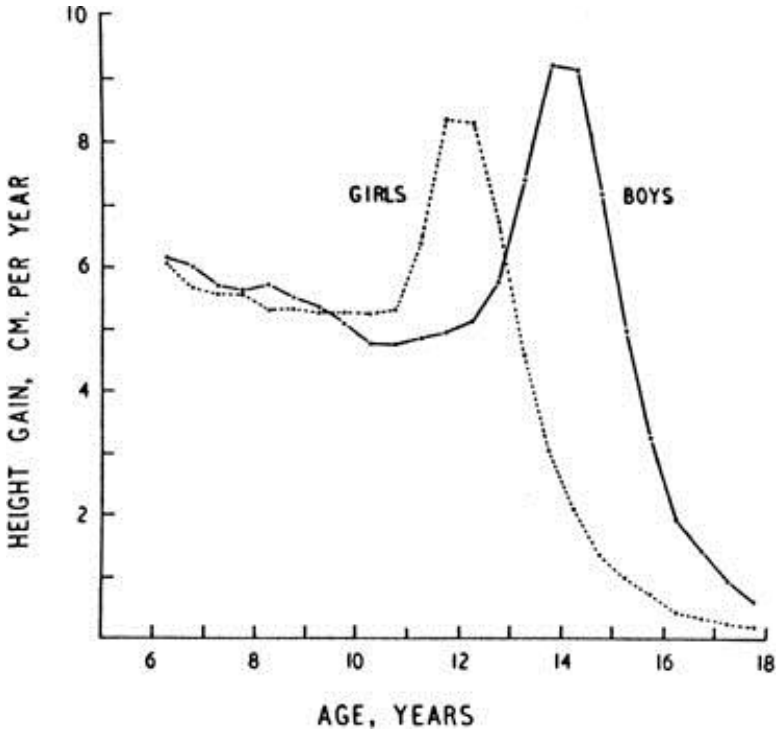

Figure 1.1 Typical growth velocity curve from Tanner, 1962.

Pubertal onset is marked by the re-initiation of the gonadotropin-releasing hormone (GnRH) pulse from the hypothalamus, which is active in infancy but remains quiescent during early and mid-childhood. The brain may inhibit the GnRH pulse during early- and mid-childhood and be released from inhibition around puberty. GnRH stimulates the production of the gonadotropins luteinising hormone (LH) and follicle-stimulating hormone (FSH), which are also released as a pulse. LH and FSH then act on the gonad (Lipson, 2001). In girls they activate the production of steroids in the ovary, which results in oestrogen release. As well as growth and development to give girls feminine traits like

shapely hips and thighs, breasts and maturing external genitalia (Tanner, 1962; Lipson, 2001), the steroids produced in the ovary feed back to the pituitary and hypothalamus and monitor the production of gonadotropins (Jones and Lopez, 2006)(See figure 1.2).

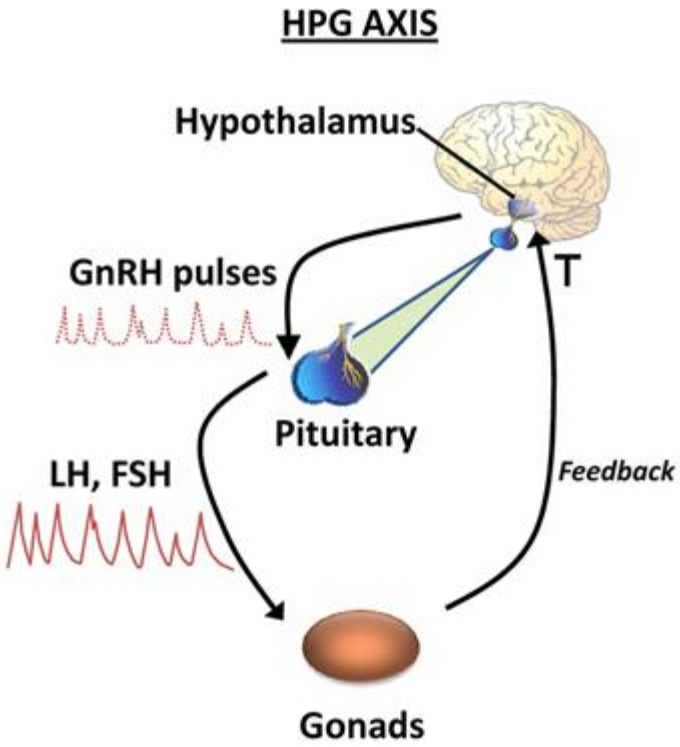

Figure. 1.2 HPG axis adapted from Jameson, 2007

During childhood the hypothalamus is extremely sensitive to oestrogens and androgens. Circulating steroid hormones therefore have a negative feedback effect on the hypothalamus, blocking production of GnRH. In concert with the release of inhibition on GnRH production, it is theorised that the hypothalamus behaves as a gonadostat and increases the set point for steroid sensitivity. As GnRH is produced and the resultant gonadotropins stimulate the maturation of

the ovary and steroid production, it takes an increasingly higher level of steroid hormones to inhibit the release of pulsatile GnRH (ibid).

Oestradiol is also capable of performing a positive feedback effect on the pituitary. In later puberty, sometime before menarche, levels of oestradiol in the blood cause a surge in LH and FSH production. This surge is responsible for ovulation in adult women. The surge will not occur in early puberty even in the presence of high oestrogen levels, and may represent the maturation of the pituitary, which is now capable of storing and producing a critical level of gonadotropins to create a surge. When the surge is great enough it is responsible for first ovulation following menarche (Lipson, 2001; Jones and Lopez, 2006). The development of the positive feedback loop requires that the sensitivity of the negative feedback system has decreased enough to allow GnRH and gonadotrophin levels to increase rather than fall as oestradiol concentrations are rising (Apter, 1997:16).

During early puberty, LH and FSH primarily pulse at night and increase in concentration in line with maturation (see figure 1.3). In late puberty and adulthood the gonadtrophins also pulse during the day and the diurnal pulsatile pattern disappears. Regular daytime LH pulses and amplification of night time pulses are closely related to the onset of breast development (Apter et al., 1993).

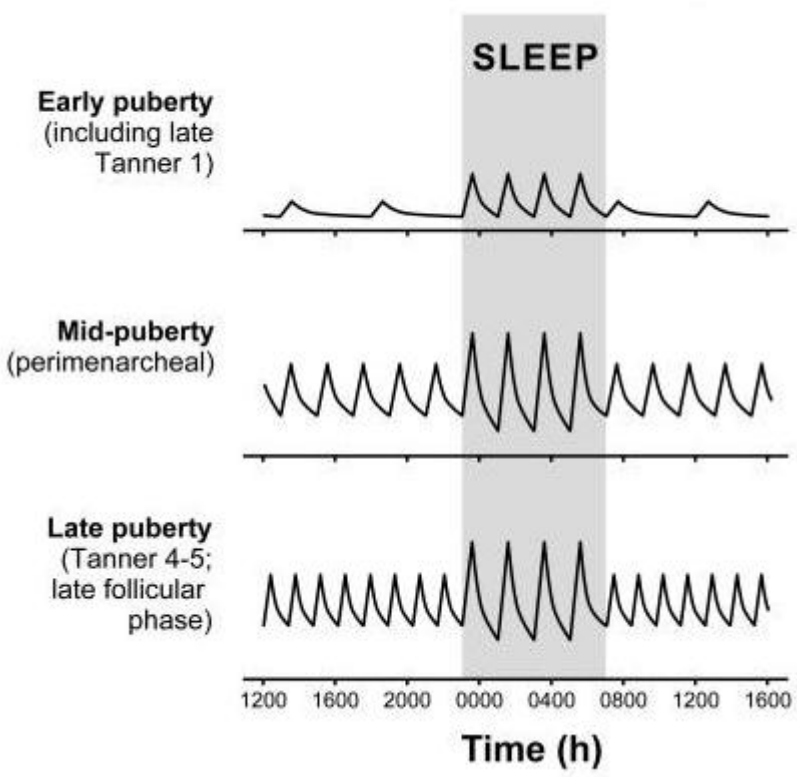

Figure. 1.3 Daily GnRH pulses across the pubertal period (from McCartney, 2010).

Pubertal onset: re-initiation of the GnRH pulse

While the role of the GnRH pulse is central to pubertal onset, there is uncertainty as to the stimulus that acts on the hypothalamus to re-initiate the pulse from an inactive state. It has been suggested that the signal is suppressed by the central nervous system (CNS) and a gradual desensitisation to the factor that blocks the signal allows for the switch (Conte et al., 1975). In fact, ultrasensitive immunofluorometric assays have detected LH and FSH in girls around 3 years prior to puberty, which suggests a gradual increase in activity of the hypothalamic-pituitary ovarian (HPO) axis during late childhood (Mitamura et al., 2000).

There has long been investigation into a number of environmental factors that could be responsible for pubertal onset. These include: family size (Hulanicka, 1989), climate (Zacharias and Wurtman, 1969; Papadimitriou, 2008), altitude

and light (Zacharias and Wurtman, 1969), pheromones (Joseph *et al,* 1977; Stern and McClintock, 1998), father absence/stepfather presence (Ellis and Garber, 2000) psychosocial stress, (Draper and Harpending, 1982; Belsky *et al.,* 1991; Hulanicka, 1999,2001; Ellis and Garber, 2000) parent-child distance (Steinberg, 1988) endocrine disrupting chemicals (EDCs) (e.g. Colborn and Dumanoski, 1996), and above all weight status (e.g . Reynolds, 1946; Frisch and Revelle, 1970; 1971; Adair and Gordon-Larsen, 2001; Kaplowitz, 2001; Anderson *et al.,* 2003; Demerath *et al.,* 2004).

In the earlier literature that attempted to understand the factor responsible for the resumption of the GnRH pulse, two prevailing theories of GnRH initiation have been debated. The first from Frisch and Revelle (1970, 1971) (the Critical Weight Hypothesis) claimed that a body weight of 48kg must be achieved to signal that the female body is capable of beginning reproductive function. There was little evidence to support a threshold theory before it was posited, but as with much literature on the subject, it relied upon the importance of nutrition in the maintenance of reproductive function. The second theory, proposed by Ellison (1981: 337), relies on skeletal development to signal sufficient maturity for the onset of puberty in females. He states that if a critical weight must be attained at any growth rate, then variance in weight at menarche must be less than at a given interval before menarche. Ellison found that height decreased in variance before the menarcheal threshold (Ibid). Simmons and Greulich (1943) had previously stated that skeletal age is a strong determinant of menarche, and Ellison went further to highlight the importance of pelvic dimensions in the ability to deliver a baby through the birth canal, and a threshold argument does not suitably account for these conditions (Ellison, 1982). There is strong selection on the pelvis to be broad and flat, and there are associations between biiliac width and menarche (See Worthman, 1993).

It is possible that both weight and skeletal growth determine age at puberty. As such, energetic reserves (activity levels and energy intake relative to size) have more recently been proffered as strong determinants of maturation (e.g. Rogol et

al., 2002; Ebling, 2005). Body composition and energy balance are important indicators of the body's capacity to maintain reproductive function. A theory of energetic reserve builds on the discovery of the neuroendocrine hormone leptin in 1994, which was then considered to be the elusive pubertal trigger. Leptin is produced in white adipose tissue proportional to energy reserves. Levels of leptin then signal these reserves to the hypothalamus via a feedback mechanism (Zhang et al., 1994). There are leptin receptors in the hypothalamus that synthesize GnRH, and it has been found that those individuals deficient in leptin fail to initiate puberty (Ong et al, 1999). However, despite these strong physiological links, evidence for a sequential chain of events starting with leptin production and leading to GnRH secretion has yet to be found. This indicates that either another link in the chain is missing, or other mechanisms are responsible for monitoring energy balance with regard to pubertal onset. Leptin may be the 'metabolic gate" that allows these actions to proceed if energetic conditions are suitable (Cheung et al., 1997).

Most recently neurokinin B - a peptide and member of the substance P-related tachykinin family - has been proffered as another possible pubertal trigger since it is highly expressed in hypothalamic neurons (Topaloglu et al., 2009). Again, there is no concrete evidence that neurokinin B performs the role of a trigger, but it is associated with loss of function in cases of hypogonadotropic hypogonadism or decreased function of the gonad (ibid). Neurokinin B may also affect levels of the hypothalamically expressed peptide kisspeptin, which has a direct effect on GnRH release, and therefore the gonadotrophes (ibid).

A large degree of variation in age at pubertal development is probably the result of diet and nutrition. Weight status plays a central role in the *maintenance* of adult reproductive function (Ellison et al., 1993; Jasienska, 2001), and this would logically lead to assumptions about the role of nutritional availability in the *onset* of reproductive function. Excessive exercise (Ellison, 1994), weight loss (Ellison et al., 1993), extreme weight gain (Rachon and Teede, 2009) and, in non-contracepting societies, lactational amenorrhoea (Vallegia and Ellison, 2009) are

all energy-related factors that can affect adult ovarian function. Reiter and Grumbach (1982) determined that, since altered nutritional availability is implicated in both normal and diminished menstrual states, this is evidence of its role in onset of puberty. However, Parent et al (2003) state that simply because nutrition may affect, or be influential in, disorders of puberty, it isn't necessarily for the onset of female pubertal development. Despite this caution it is hard to ignore how well the role of weight status as an energetic cue sits within the study of pubertal onset and probably accounts for the continued associations made between weight, nutrition and pubertal onset in the literature.

While the endocrine system and CNS oversee the processes of maturation, it is well established that there are strong environmental and genetic determinants of the timing of pubertal onset in girls. Genetic determinants of pubertal onset have been elucidated from both inheritance studies (e.g. Kaprio et al., 1995) and targeted investigations into the role of particular genetic loci (Gajdos et al., 2010). The environment continually mediates human genetic potential for linear growth (Rogol et al., 2002), and mediates the relationship between the genetic potential for earlier or later reproduction, and environmental conditions. Given the genetic similarity within the population genetic influence is likely not only between parents and daughter, but also within a population. But the greatest degree of inter-population variation seems to be the result of nutrition, disease burden and immune cost, energetic output, and cultural practices; all are, of course, elements that contribute to the ecology of a population and an individual, and therefore determine the energy available to the individual to grow and mature.

Measuring puberty

Such is the human fascination with maturation, puberty, and rites of passage (e.g. Boas, 1892; Van Gennep, 1909; Tanner, 1962; 1968; 1969; 1978; Eveleth and Tanner, 1990) it is no surprise that pubertal development has come under the lens of biomedicine. Biomedicine considers puberty relative to norms and pathology rather than in an adaptationist view of body-environment interactions

where energy allocation is regarded a driver in variation (e.g. Worthman, 1999). As such, western clinical medicine has developed various scales where the milestones of female pubertal development fall within pre-determined time slots. This view relies somewhat on pubertal scales that describe the visually discrete stages of puberty. In human females, puberty involves the initiation of the menstrual cycle and outward appearance of breasts and shapely hips, as well as the growth of both pubic and axillary hair (Tanner, 1962; 1978). These outward signals are an indication of ovarian and uterine development and therefore serve as a proxy measure of reproductive readiness. These visual categories have been narrowed down into a series of visually measurable or descriptive stages in a number of relevant scales.

Tanner and Whitehouse studied both male and female children in a Hertfordshire children's home - called the Harpenden Children's Home - from 1948 until 1971 (Tanner, 1981). In addition to anthropometric measures, each child was photographed at successive points throughout the pubertal period. The result was a photographic scale that indicated 5 discrete stages of puberty in both males and females that could be used as a guide for physical examination (See figure 1.4 and descriptions).

Based on observations made by Whitehouse the stages for breast development are as follows:

Stage 1: Pre-adolescent; elevation of the papilla only.

Stage 2. Breast bud stage; elevation of the breast and papilla as a small mound, enlargement of areola diameter.

Stage 3. Further enlargement of breast and areola, with no separation of their contours.

Stage 4. Projection of areola and papilla to form a secondary mound above the level of the breast.

Stage 5. Mature stage; projection of papilla only, due to recession of the areola to the general contour of the breast.

(Marshall and Tanner, 1969).

Stages for pubic hair growth are as follows:

Stage 1. Pre-adolescent; the vellus over the pubes is not further developed than that over the anterior abdominal wall, i.e. no pubic hair.

Stage 2. Sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, appearing chiefly along the labia…

Stage 3. Considerably darker, coarser, and more curled. The hair spreads sparsely over the junction of the pubes.

Stage 4. Hair is now adult in type, but the area by it is still considerably smaller than in most adults. There is no spread to the medial surface of the thighs.

Stage 5. Adult in quantity and type, distributed as an inverse triangle of the classically feminine pattern. Spread to the medial surface of the thighs, but no up the linea alba or elsewhere above the base of the inverse triangle.

(Marshall and Tanner, 1969)

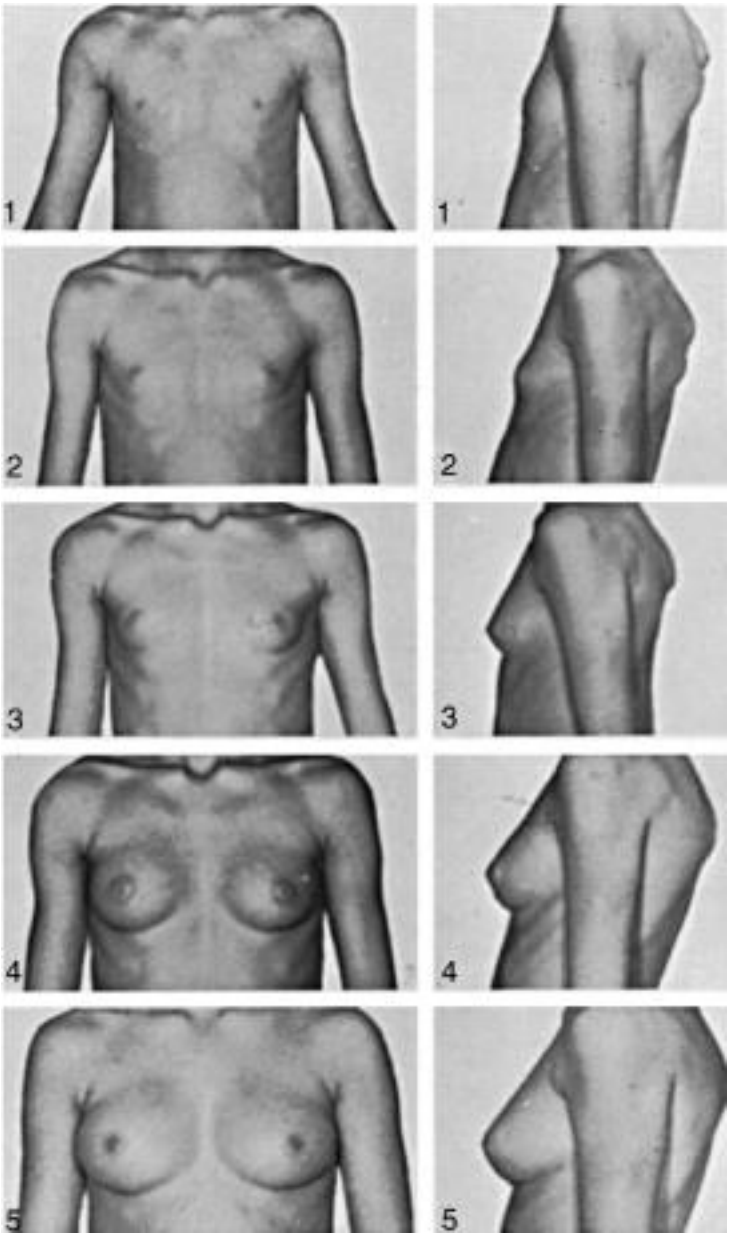

Figure. 1.4 Breast stages from Tanner, 1969.

In addition to these photographs, James Tanner described the female pubertal process as a series of events that take place at given intervals so that you can generally expect one to occur at a given point after the previous. Tanner and Whitehouse found that either breast development (thelarche) or pubic hair growth (pubarche) signalled the onset of female pubertal development, but that the two were more or less synchronous. They also determined that menarche was likely to occur at around breast stage 3, following PHV, and the pubertal process would finish at stage 5 (mean 15.33 years for breast development) (Marhsall and Tanner, 1969). The relevant literature is consistent in

demonstrating that menarche takes place after PHV. As the result of extensive work by Tanner and Whitehouse on the Harpenden Growth Study from the late 1940s into the 1970s, funded by the then Ministry of Health, we are able to understand and recognise the course of pubertal maturation. Moreover, we can determine when a child has both begun and finished pubertal development.

The Tanner-Whitehouse scale is still widely considered the gold standard in puberty studies. The clearly marked stages make it easy to categorise groups of adolescents and to understand where an individual lies on the scale. They can be categorised as an early, late, or normal developer depending on where they lie on the scale in relation to their peers. However, it is important to clarify that the Tanner-Whitehouse scale and those like it are not a measure of age or a tool for age estimation. The stages may be a useful tool in understanding the developmental progress of an individual relative to their population norm, but this is more a descriptive measure of "later" or "earlier" maturity relative to a mean or median measure.

Tanner's work gives biologists a standard from which to start to understand the limits of "normal" pubertal development and for charting progress in the individual. These variations are discussed for both males and females in subsequent publications (Marshall and Tanner 1969; 1970). Although the Tanner Scale represents "normal" pubertal development from the 1950s when the data were collected, the continuing benefit of references like this is that we can still understand female pubertal development, and it informs us as to how pubertal maturation may be diverging from an established reference scale.

It is important to note that the Tanner Scale may not have been nationally representative, as Tanner himself suggests in 1969. The Harpenden children came to the home from diverse backgrounds, with varying degrees of information on their early childhood. It is likely that some could have come to the home from poor backgrounds and may have been malnourished on arrival or at points during their childhood. Although the Harpenden children received good

care when in the Home, early childhood exposures to growth insults would have had a huge impact on their growth and maturation trajectory, which suggests that the Tanner scale may be inherently biased. Moreover, the Harpenden children acted as test cases for the nutritional content of school meals. The meals in the home were of course paid for by the state, and when budgets were overstretched one month, meal budgets had to be stretched equally to cope the next month (Howard, 2007). This could mean that the Harpenden children were occasionally subject to under-nutrition. However, the process of pubertal events as described for the Harpenden children remains the gold standard by which maturation is understood in both clinical and biological settings.

The Pubertal Development Scale (PDS) is another widely used measure of puberty (PDS) (Petersen et al., 1988). The PDS is particularly useful as a non-invasive method of assessing pubertal development when clinical examination may not be possible. The verbal-response questionnaire is completed in an interview situation and individuals respond to questions about body hair, growth of secondary sexual characteristics and, in the case of girls, age at menarche. The scale is also a measure of puberty in reference to peers where individuals answer questions on the extent of their development relative to friends and peers, for example, whether they are growing in height at the same rate as their friends (Petersen et al., 1988). While the PDS might be useful as a means to understand how children in a given environment are developing, it does not provide sufficient opportunity to understand how far along the process an individual sits since their responses are somewhat subjective. As an example, some children might find it hard to compare themselves to others or recognise what is more or less mature, or to know what constitutes a lot or a little of pubic hair development. Pubic hair growth may be moderate, but to an individual who has just begun pubarche it may seem much more significant. However, there is evidence of agreement between the PDS and Tanner stages (Bond et al., 2006), which suggests that they both remain useful and reliable sources of information about pubertal development.

Other tests of maturity involve touch, such as palpation of the breast, or even ultrasound of the internal reproductive organs. An accurate measure of pubertal onset is to measure the GnRH pulse, which indicates whether the GnRH pulse generator has reinitiated (Wu et al., 1996). Girls can self-report with photos or drawings from the Tanner Scale if invasive tests or responding to descriptions may make them uncomfortable, or is culturally unacceptable. It is clear therefore that researchers are able to monitor and recognise pubertal stages under a number of conditions.

The secular trend in female pubertal development

Research has highlighted the effect of food abundance and physical inactivity in the modern environment of developed nations on female pubertal development. Over the course of the last half-century, average age at menarche in the UK has fallen to around 12.9 (Rubin et al., 2009), and to 12.5 in the USA (Anderson et al., 2005) (Table 1.1 lists recent comparable data for pubertal maturation from a number of other developed countries.); over that same period both countries have seen steep rises in rates of obesity. Moreover, those most vulnerable to overnutrition are maturing faster than even their peers. For example, mean age at menarche in Germany has been reported as 12.8, but the mean age among overweight girls is 12.5 compared with 12.9 in normal weight peers (Bau et al, 2009).

Table 1.1 Pubertal maturation in developed nations. *median

Country	Year	Age at menarche	Age at B2	Age at PH2	Source
Denmark	1991-1993	13.42	10.88	11.29	Juul et al, 2006
England: Avon	1991-present	12.93	10.14	10.92	Rubin et al, 2009
France	2006	12.80			Gaudineau et al, 2010
Berlin	2006-2007	12.80			Bau et al, 2009
Athens	2006	12.29	10.00*		Papadimitriou et al, 2008
Italy: National		12.40			Rigon et al, 2010
Ireland (Eire)	2006	12.53			O'Connell et al, 2009
Poland:Wroclaw	1996-1997	12.70			Koziel and Jankowska, 2002
Australia (Raine)	1989-present	13.00*			Sloboda et al, 2007
Canada	2000-2001	12.72 12.67*			Al-Sahab et al, 2010
USA	1999-2002	12.34			Anderson and Must, 2005
Hawaii: Honolulu		11.57			Novotny et al, 2003
Taiwan	1999	13.00*			Chang and Chen, 2008
China (Urban Han)	2005	12.60			Song et al., 2011

Historically, documented age at menarche has been variable. Translations from ancient Indian epics from around 300BC-AD300 describe age at menarche at around 12 years (Datta and Gupta, 1981), which is slightly earlier than contemporary Europe (Parent *et al.,* 2003). Girls were said to be around 14 years of age at menarche in the European Middle Ages, with information from ancient Rome claiming girls as young as 11 or 12 often became mothers. This rose to around 17 years at the beginning of the 19th century in Europe (Tanner, 1981). Reproductive biologists also have almost a century's worth of data from the developed world that points to a significant downward trend in age at pubertal onset- often called the secular trend (See Eveleth and Tanner, 1976/1990; Wyshak, 1982).

In 19th century Europe onwards, industrialisation brought improvements in health, nutrition, sanitation and living conditions, resulting in a downward secular trend for age at menarche reducing around 4 months per decade from 16.5-17 years in 1830 to around 13 years by 1960 (Tanner, 1962; 1981). More recently, evidence from the USA has demonstrated a downward secular trend in the age at which girls now *begin* pubertal development compared with the preceding generation (Herman-Giddens et al., 1997; Kaplowitz and Oberfield, 1999; Parent et al., 2003; Anderson et al., 2005).

A discussion of modern clinical understanding of precocious puberty by Parent et al (2003) described an increase in the numbers of girls showing signs of pubertal onset – either thelarche or pubarche - at ages typically considered precocious, but where no pathological cause could be found. Concerned parents were bringing girls as young as 6 to the doctor for examination when they showed these characteristics of sexual development. Two seminal papers documented these phenomena and provided the impetus for an analysis of relevant longitudinal data on girls in the USA (Herman-Giddens et al., 1997; Parent et al., 2003) in order to understand the extent to which there is a shift in the age that girls begin the pubertal process. Parent et al. (2003) recommend a

change in the USA in the age at which clinicians determine puberty to be precocious in the absence of any underlying pathology or endocrine abnormality, which would be under 7 for white American females, and under age 6 for African American females who are known to develop relatively earlier (Parent et al., 2003).

Herman-Giddens et al. (1997) and Schubert et al. (2005) analysed cross-sectional US data from 2104 girls attending specialist clinics and around 17,000 girls in the National Health and Nutrition Examination Survey (NHANES) III data set, respectively. They found that overweight girls were more likely to begin pubertal development earlier than normal weight peers. Further patterns of downward secular trends have since been demonstrated in other developed countries. Much of the literature on this issue similarly considers the concurrent rise in overweight and obesity among children to be a primary explanation for this developmental shift. Evidence from the USA and Denmark, as well as recent data from the UK, suggests that earlier pubertal onset is associated with measures of higher weight status from birth throughout childhood (Anderson et al., 2005; Aksglaede et al., 2008; Christensen et al., 2010a; 2010b).

Given the relationship between body weight and fecundity it is a logical consideration that there may be a similar relationship between body weight and pubertal onset. Although, as previously stated, ovarian maturation is not the same as normal ovarian function (Freedman et al., 2003), there are likely to be similar mechanisms of energy allocation whereby the energetic requirements of pubertal maturation may be met at considerably younger ages if girls are heavier or fatter since they would incur fewer nutritional insults than more energetically-stressed girls who begin the process of maturation at a younger age. In an environment of prolonged positive energy balance the threshold that determines when an individual is capable of reproductive function may occur much earlier than in an environment with limited energy sources and a high energy expenditure. However, there is little evidence of the mechanisms involved in these processes.

It has been proposed that age at maturation may be relative to the length of time spent in positive energy balance since energy allocation towards maturation could occur sooner. In fact, both Rogol et al (2002) and Ebling (2005) highlight the importance of energetic reserves and energy intake relative to size, as indicators of the body's capacity to maintain reproductive function. They suggest that long-term measurement of energy intake versus expenditure could signal when pubertal onset would maximise reproductive potential.

The mechanisms of earlier puberty may also be mediated by lifestyle and environment (epigenetic factors); or genetics, which could explain some of the disparate rates of maturation among different ethnic groups. In the USA, African American and Hispanic girls are most likely to begin developing early, but white American girls are also developing earlier than in previous decades (Adair and Gorden-Larsen, 2001; Demerath et al., 2004; Anderson and Must, 2005).

However, there is some debate over the degree to which age at first menstruation might be accelerating, or whether the age at this milestone remains stable while age at pubertal *onset* is instead accelerating in response to overweight. For example, the NHANES III data from the USA showed a 2.5 month drop in age at menarche between 1963 and 1994 (Anderson *et al.,* 2003), whereas a Danish study found that girls from the same region of Denmark who were recruited 15 years apart reached pubertal onset a full year younger in the most recent cohort, but menarcheal age remained unchanged (Aksglaede et al., 2009; Sorensen et al., 2010).

While there are cases of stationary menarcheal age over generations, as well as, in some cases, increases in menarcheal age (a reversal of the trend over multiple cohort generations (Nichols et al., 2006)) from various populations, there is some evidence for a continued secular trend in age at menarche in the USA. An expert panel (Euling et al., 2008) agreed that data are sufficient to deem that

there is an earlier onset of breast development *and* menarche based on longitudinal data. This might reflect either scope for further investigation into the USA as a special example, or the necessity of further large scale studies for comparison in other populations. As such, many of the most recent studies concerned with puberty have centred their efforts on documenting both of these pubertal milestones.

The evidence for changing age at menarche is mixed, but there is overwhelming evidence that age at pubertal onset is accelerating. Not only is puberty beginning earlier, but the process is deviating from the well-known model of "typical" pubertal development first described by James Tanner, whereby thelarche and pubarche are virtually synchronous (Tanner, 1962; Marshall and Tanner, 1969). It is typical that both events (thelarche and pubarche) occur within a single year, although Tanner found a lag of up to two years before pubic hair development in exceptional cases (Tanner, 1962).

In response to increased fat in the diet, low activity levels, and mechanisms of positive energy balance, it appears that now the pubertal process begins with the distinct development of breasts *or* pubic hair, rather than the virtually synchronous development of both (Biro et al., 2003; Dunger et al., 2005; Christensen et al., 2010a; 2010b). More specifically, there is an emerging trend for earlier breast development among obese and overweight girls born appropriate for gestational age (AGA) (Herman-Giddens et al. 1997; Schubert et al., 2005).

The classic Tanner model is a process whereby breast development begins, on average, just before the eleventh birthday, with pubic hair growth following soon after (Tanner, 1989, Chapter 5). In contrast, Herman-Giddens et al (1997) and Schubert et al (2005) note asynchronous development with breasts developing well before the eleventh birthday, in some cases, and certainly a significant period before pubarche. While asynchrony was represented in Marshall and Tanner's original data from the Harpenden Children's Home, it represented an

overall minority. However, it seems now that this asynchrony is becoming increasingly commonplace among heavier girls. Indeed, in a study of girls in the USA Biro et al (2003; 2008) found that girls were developing either breasts or pubic hair significantly earlier than the other respective character. Moreover, they found that girls who were overweight were more likely to enter puberty via thelarche (ibid).

Most recently, findings have been reported from the Avon Longitudinal Study of Parents and Children (ALSPAC) in the UK, that girls who are overweight at age 8 are more likely to enter puberty via thelarche. The median age at thelarche among this cohort is 9.4 years (Christensen et al., 2010; 2011). This median age is, significantly lower than the age of 11 that Tanner and colleagues reported as typical from their UK cohort from the 1950s. Christensen et al. (2010a; 2010b) also noted that, despite age at onset of breast development becoming earlier, a similar drop in age at menarche was absent. What these results indicate is that, in the UK, there is a lengthening of pre-menarcheal pubertal development, which is at odds with the Tanner-Marshall model of the pubertal process.

However, techniques for examining onset of breast development are often visual or descriptive and, without physical palpation of apparent breast tissue, it is possible to mistake fat accumulation of overweight girls for the appearance of a breast bud (Biro et al., 2010). Despite this complication in identifying true breast tissue from fat tissue there is still considerable support for the role of overweight and obesity in accelerating pubertal onset (e.g. Biro et al., 2010; Christensen et al., 2010a; b)

While overweight is a risk for early thelarche in girls, there is a particular risk for early age at pubertal onset via pubarche for girls born small for gestational age (SGA) who also experience weight gain in the form of catch-up growth during childhood (Ibanez and Zegher, 2006). Ibanez et al., (2006) even go so far as to say that the greatest risk factor for girls with a low birth weight followed by catch-up growth is precocious pubarche. Ibanez and colleagues have also

highlighted the particular risk of asynchronous development via pubarche to girls born SGA as a result of prenatal growth restraint, with significant catch-up growth and high adiposity in childhood (ibid). They associate the link between catch-up growth and early menarche with mechanisms of insulin resistance and hyperandrogenism (Ibanez and Zegher, 2006). Girls born SGA are also at more at risk of central adiposity, which seems to be a particular risk factor for early maturation (Ibanez and Zegher, 2006; Ibanez et al., 2006).

It seems that weight status, diet and energetic availability are universally understood to be strong predictors of the pubertal maturation schedule, and indeed capable of altering it. Ovarian function is so closely related to diet and nutrition that energy availability is a strong determinant of investment in reproduction. The mechanisms that signal energy availability are also closely linked to metabolic function.

It is possible that nutrition may influence maturation schedules even before birth. Maternal nutrition may be imprinting on the foetus to determine development and reproductive maturation (Lipson, 2001). This may affect the foetal hypothalamus, possibly via epigenetic effects. Despite evidence for the effects of overweight and obesity in early and mid-childhood on maturation we still have limited knowledge of the mechanisms behind this relationship. Fat is an organ about which we still know relatively little (Pond, 1998), and the relationship of fat to reproductive onset and function is a complicated one that involves a number of neuroendocrine and other regulatory hormones.

Beyond the obvious thermoregulatory and energy storage capacities of fat tissue (Pond, 1998; Cannon and Nedergaard, 2004), it has a number of other actions within the body. For example, it was only in 1994 that leptin was understood to be produced in adipose tissue (Zhang et al., 1994). Leptin is a neuroendocrine hormone that signals fat reserves to the brain in order to maintain energy availability for proper bodily functioning. Leptin is involved in numerous other processes besides appetite regulation, like promotion of growth in the ovary,

immune function, and inflammatory responses (Raynor and Trayhurn, 2001). The unifying role of leptin in these processes is energy allocation. Where energy is abundant leptin signals availability to all of these bodily systems where leptin receptors are numerous. When energy is scarce, the reduction in leptin signals to other systems to reduce output or to cease altogether (ibid). Leptin is therefore central in translating the signals of energy availability to body systems to maintain basic functions during times of scarcity.

With regards to puberty, there are many leptin receptors in the hypothalamus that synthesize GnRH, and it has been found that those individuals deficient in leptin fail to initiate puberty (Ong et al, 1999). Given the role of leptin in indicating energetic reserve it is thought that it has a permissive role in puberty by signalling the presence, or indeed lack, of a favourable environment in which to initiate pubertal development (Cheung et al., 1997).

There are other examples of interaction between growth hormones, appetite regulators and pubertal development in females. These metabolic hormones impact the HPO axis and signal how available energy will be apportioned between growth, maintenance and reproduction. IGF-1 stimulates LH-RH (luteinising hormone-releasing hormone) (Lipson, 2001). Insulin, IGF-1 and leptin levels all rise during puberty. IGF-1 and insulin are related to height velocity and concurrent rise in steroid levels at pubertal onset (Apter, 1997; Smith et al., 2007). Insulin, IGF-1 and leptin receptors have all been found in ovarian cells (Poretsky et al., 1999, Pirwany et al., 2001). Insulin is important in oocyte growth and follicular maturation. Moreover, reduced leptin and decreased insulin are associated with reproductive dysfunction (ibid).

Insulin, leptin and IGF-1 are likely to serve as indicators of energy to the reproductive system (lipson, 2001). Insulin, leptin and IGF-1 receptors have all been found on ovarian cells. Insulin specifically is involved in the maturation of the oocyte and follicle. Moreover, increased insulin levels are known to decrease levels of sex hormone-binding globulin (SHBG), which binds to oestrogen; the

lower the levels of SHBG, the greater the bioavailability of oestrogen. Additionally, insulin and IGF-1 are associated with height velocity, so could have a strong relationship with the pre-pubertal growth spurt. The relationship between insulin, leptin and ovarian function provides possible mechanisms for the division of finite energy among the body's primary functions.

The literature has concluded that these hormones play a monitoring role rather than behaving as the trigger for pubertal onset. It is likely to be interactions between axes, rather than individual effects, that have the greatest impact on regulating maturation (Rogol et al., 2002). This may be the result of long-term monitoring of energy intake and energy reserves to determine the period of time spent in positive energy balance, which could signal good condition for the onset of reproductive function, thereby producing the most recent effect of accelerated breast development.

Considering diet, there might also be a response to periods of food insecurity. There is evidence for seasonal variation in child growth, whereby children grow more in the spring compared to the autumn (Rogol et al., 2000). The growth spurt, characterised by PHV, is the first signal of pubertal development, and may therefore be delayed or accelerated in response to seasonal fluctuations in food, and therefore energy availability. Moreover, premature thelarche in girls in Jerusalem was seen significantly more often in spring than any other seasons (Boneh et al., 1989). Given that there may be sensitive periods during childhood where the CNS and HPO could respond to environmental cues to food abundance or paucity this is likely an adaptive response, which would restrict the opportunity for maturation at times where the trade-offs incurred to the individual by maturing while there is food scarcity, or limited types of foods available, would adversely affect their overall condition, and promote earlier pubertal onset in times of abundance.

Factors associated with early menarche

Endocrine markers

There are particular hormonal markers that are associated with earlier development. Early menarche results from higher oestradiol pre-puberty (Vihko and Apter, 1984; Tam et al., 2006). Girls with earlier puberty have a decreased sensitivity of the hypothalamic-pituitary unit to circulating steroids (Apter and Vihko, 1985). Early maturity is evidence of a more profound desensitisation in hypothalamic pituitary sensitivity. The level of HPO sensitivity may well be set before birth and could represent a critical period of growth, which could be affected by maternal nutrition to indicate likely early childhood conditions (Barker et al., 1995). Even before early menarche, those girls are characterised by higher serum FSH and oestradiol concentrations than girls who experienced menarche post-thirteen years of age (Vihko and Apter 1984). As well as an early rise in oestrogen levels, early menarche is also marked by higher baseline oestrogen levels throughout the resulting menstrual cycles, when compared with peers (McMahon, 1982).

Adolescent sub-fecundity

Earlier age at maturation, and specifically early age at menarche is linked with a shorter period of adolescent sub-fecundity (Vihko and Apter, 1984). It seems that girls who mature earlier more quickly shift to ovulatory menstrual cycles and are therefore able to conceive quicker than girls who mature slightly later. Differences in the frequency of ovulatory cycles disappear in the late teenage years (ibid). However, early menarche can result in early first birth and LBW babies. While this lends support to the good nutrition hypothesis that well-nourished girls are developing early, but may produce smaller babies since they have yet to finish growing, shouldn't they also be producing heavier babies? Coall and Chisholm (2003) suggest that the truest indictor of the good nutrition hypothesis would be higher birth weights and babies who are more likely to survive. They go on to suggest that smaller babies born to younger mothers may be explained by a more complicated evolutionary basis to early menarche (ibid). However, it seems somewhat self-evident that earlier menarche and low birth

weight can be explained in a very straightforward evolutionary sense since girls will increase their total fertility by beginning to reproduce sooner, and have enough resources not to compromise to also continue to grow to their adult height during this time.

Girls who are fecund earlier also seem to go through the stages of the pubertal transition quicker than later-maturing girls. Girls who are early maturers experience quicker transition between breast and pubic hair stage 2 and menarche (Apter and Vihko, 1985). The rapid sequence is likely related to high serum oestrogens (ibid). This might be evidence of a slightly faster reproductive schedule overall supported by favourable energetic conditions.

Height growth

Those girls who do mature earlier tend to lose out in final height. They have a shorter period of time before the growth plates of the long bones fuse at the end of puberty (He and Karlberg, 2001). Later-maturing girls spend longer in pre-puberty and therefore gain more in height before the long bones finish growing, even though early-maturing girls are taller than peers at pubertal onset (Simmons and Greulich, 1943).

Adoption and migration

A change in environment does not just accelerate maturation; there is evidence to suggest it has an impact on the baseline levels of the hormones that control pubertal development. Girls who are adopted from India by Swedish families have steroid hormone levels above those of peers born and raised in Sweden to Swedish parents. It is thought that the body responds to this change and quickly invests in reproduction since a favourable environment will better support pubertal development and reproduction (Proos et al., 1991; 1993; Virdis et al., 1998; Domine et al., 2006; Teilmann et al., 2006). This effect is pronounced depending on age at migration. For example, girls who move to London from Bangladesh after the age of sixteen have relatively low adult steroid hormone

levels analogous to middle class Bangladeshi women in Bangladesh, whereas those who move before age sixteen show a similar response to those girls adopted to more favourable conditions: their hormone profiles as adults look more like peers born and raised in the London to British parents, and in some cases their steroid hormone profiles can be higher still, and pubertal development earlier, than populations norms for the UK (Nunez de la Mora and Bentley, 2007).

In delaying maturation girls have the opportunity to gain more in height and weight before investing their limited resources in pubertal onset, although their adult body size is often smaller than population averages for well-nourished populations, who have been growing bigger and taller with improvements in sanitation, disease control and far less uncertainty in food availability than is typical in subsistence populations (Tanner, 1981). Delayed maturation is accompanied by other reproductive decisions that lower energy availability is able to support. Environmental cues to energy availability, energy uncertainty and immune compromises impact baseline steroid hormone levels such that women who mature in less favourable conditions have lower baseline levels than women from more favourable environments (Ellison et al., 1993; Nunez de la Mora et al., 2007). There is evidence to suggest that these cues occur prenatally (Sloboda et al., 2007), and during early childhood, particularly before adrenarche (Nunez de la Mora et al., 2007). It is probable that cues from many pre-adult developmental periods work in concert to support reproductive effort.

Nunez de la Mora and Bentley (2008) describe ecological conditions as a bioassay of the energy available to the body. As discussed, ecological conditions during foetal life can influence adult production of reproductive hormones; the purpose of which is to reserve energy later and to ensure that an individual's energetic outlay closely matches their blueprint for reproductive function and the conditions they are likely to face during maturation and adult reproductive stages (see Nunez de la Mora and Bentley, 2008). Phenotypic plasticity is likely to have evolved as a result of the uncertain environment in which humans

evolved. A flexible reproductive strategy is the evolutionary product of that plasticity, which responds to various ecologies in order to optimise reproductive fitness.

Psychosocial environment and the absent father-present stepfather paradigm

There are elements of the psychosocial environment that can impact female pubertal development. Specifically, the level of stress, instability and unpredictability in the environment can influence life history schedules. Belsky, Steinberg and Draper (1991) proposed differential age at maturation depending on the stress, or lack thereof, in a girl's environment. The psychosocial environment is capable of affecting endocrine function and in turn puberty. The absence of a father or the presence of a stepfather or other paternal figure during childhood has been associated with pubertal onset and hormonal responses (Draper and Harpending, 1982; Ellis and Garber, 2000; Quinlan, 2003). This effect may be a response to both an unstable environment and the necessity to invest in reproductive effort sooner, or it may be a response to a reduction in parental investment (Alvergne et al, 2008).

First, a stepfather may provide less for a child in terms of goods and support than their biological father and, secondly, it is possible that the presence of a stepfather will reduce maternal investment in offspring since the mother is investing in her new relationship (ibid). The effect on reproductive development in girls is greater when the father is absent before the girl reaches 5 years of age. Father absence before this point, and living only with a mother after this event, are the strongest predictors of reduced age at menarche within the absent father/stepfather paradigm (ibid).

The makeup of the "modern" family is very different to the traditional family model. There are greater numbers of separation and divorce worldwide than ever before. Not only does this expose more girls to the absent father/stepfather paradigm, but also to the emotional strain of marital breakdown and associated

parental stress. All of these factors might signal instability to the individual and trigger this particular developmental response. Early onset of puberty is also predicted by father absence in high-income US families (Deardorff et al., 2011). This was either via breast development, but was more likely to manifest as earlier onset of pubic hair growth in African-American girls (ibid). Despite the secure financial circumstance of the family, the circumstance of family breakdown predicted an earlier maturation.

However, marital breakdown may also be associated with other lifestyle or social factors that are associated with, or responsible for, accelerated female pubertal development. Whether that be the absence of particular resources or emotional support as the result of marriage dissolution, or in fact a doubling of resources - and thereby the potential for calorific excess - from two separate parental households, it is too simplistic to state that marital breakdown or the relationship to males present in the home will determine the timing of puberty onset.

Family environment may serve as a measure of parental investment. Rather than simply being about the quality of the environment it is also a measure of unpredictability, which is likely to be a significant factor in age at pubertal onset. In environments of high parental investment – where predictability is likely to be high-, it can benefit the individual to prolong the developmental phase in order to increase psychosocial competencies. In environments of low parental investment it benefits the fitness of the individual to accelerate puberty in order to increase reproductive potential to capitalise on reproductive opportunities if there is the prospect of future uncertainty (Ellis and Essex, 2007: 1813). Of course, high parental investment is often associated with high resource availability, and we know that relatively well-off populations and individuals mature faster as a result. This perhaps accounts for the paradoxical earlier maturation of both girls in wealthy, well-nourished environments, as well as girls in risky, unpredictable, or resource-poor environments.

An interesting genetic component of this paradigm may be an inherited propensity to both family breakdown and early development, however this suggestion is based on the possibility of a tentative link between an variant X-linked androgen receptor inherited from the father, and increased likelihood of abandonment as well as earlier age at menarche in females (Alvergne et al., 2008). But, it is highly unlikely that control of pubertal development is single gene-dependent, or would be able to so specifically determine behaviour. More plausible is the concept of Biological Context Sensitivity (Ellis et al., 2011), which argues that retaining selection for variation in response to stressful circumstances could account for variation in age at pubertal onset among girls in various environments considered to be psychosocially stressful.

Risks of changing age at pubertal onset

The reported changes in the process of pubertal maturation indicate a lengthening of the pre-menarcheal pubertal period, which is at odds with the Tanner-Whitehouse model of events. What do these changes mean for females? Could these changes represent risks for later life?

It is difficult to know how a shift towards earlier pubertal onset will affect girls later in their adult lives. There are the obvious increased risks of reproductive cancers (Jasienska et al., 2000; Jasienska and Thune, 2001), and the possibility of co-morbidities, but there may also be a mismatch between physical and psychosocial development. Earlier puberty may increase reproductive success or represent the preferred strategy under conditions of psychosocial stress, but how does that resolve the obvious curtailment of the time available for learning and observing as well as acquiring adequate psychosocial competencies?

Earlier maturation is associated with increased number of sexual partners, but also with risky behaviours like early sexual contact, teen pregnancy, alcohol and substance misuse and unpredictable environments (Gaudineau et al., 2010). All of these behaviours have the potential to impact health, but the increased

chances of pregnancy via risky behaviours as well as early fecundity leaves girls vulnerable to obstetric and neonatal complications such as greater change of miscarriage, greater risk of pregnancy complications and higher rates of neonatal death (Fraser et al., 1995). While this is not the case for all girls, it does highlight the possibility that earlier maturation has the potential to reduce reproductive success.

If girls in developed nations, who have access to caloric excess, prefer sedentary play and activities and eat more processed foods, are undergoing puberty at an increasingly young age, what then does puberty look like in populations who are not exposed to obesity and high levels of reproductive hormones? Clinicians expect all girls to experience the same pubertal events, but do these events always follow the same pattern, at the same time under all ecological circumstances currently experienced by global populations? In order to understand the degree of variation among more disparate populations of humans, it is perhaps more beneficial to understand how lifestyle and environment may determine the onset and timing of those milestone events on which clinicians concentrate their understanding of normal. Perhaps then clinicians would be better able to recognise the degree to which evident changes in the pubertal schedules of girls from western developed nations may reflect expected human phenotypic variation as opposed to harmful pathology. In the next Chapter then, I outline the process of puberty in urbanising populations as well as subsistence level populations of both foragers and agro-pastoralists in order to understand variation in female puberty in response to different modes of production and ecological circumstances.

Chapter Two: Ecological and life history variants as determinants of worldwide variation in female pubertal development

Humans have an established schedule of life events that is unusual in comparison to the other great apes. Humans are born secondarily altricial as a consequence of locomotor constraints on female pelvic dimensions, which require a large percentage of brain growth to take place postnatally (Rosenberg and Trevathan, 1996). Equally as a consequence of these constraints, humans have a relatively extended juvenile period over which to grow, learn, and acquire skills before they begin to reproduce (Bogin 1994, 1999). Our closest relatives, chimpanzees, are born precocial and mature quickly in order to start producing young (Rosenberg and Trevathan, 1996). This significant difference in both ontogeny and maturation represents an important development in our evolutionary history. It is this difference that allows humans to spend an extended period not only growing, maturing, and learning, but also understanding the complex rules of human society and interactions.

Early maturation among females is unusual in *human* history since it deviates from a long-established life history strategy where individuals acquire social and cultural tools over an extended juvenile period. Such an extended period also provides the opportunity to practise care giving and help with siblings in preparation for future reproduction and parenting success (Worthman, 1993; Bogin, 1999). From an evolutionary perspective, the timing of puberty is the convergence of strategies evolved to minimise juvenile mortality and maximise reproductive success (ibid). In a modern industrialised environment with sanitised living conditions, antibiotics, and low selection from zoonotic disease, juvenile mortality is much reduced compared with our evolutionary past, resulting in an extended reproductive period. In the modern western environment and in contrast to most of human history, girls (unless from particularly poor backgrounds) are over-nourished and therefore capable of apportioning energy to reproductive function at a relatively early age. For many,

maturation now begins before girls are fully socially mature or independent (Gluckman and Hanson, 2006).

In other, more stressful environments girls do not typically mature as early or as fast. In forager or other subsistence populations, girls may be in marriage partnerships well before menarche. Indeed, population variation in female pubertal development is typically reflected in differences between population averages of milestone events like pubertal onset and menarche, as well as the overall duration of puberty. Worldwide variation in average age at menarche ranges from 11 in the US (Anderson and Must, 2005), to around 17 years in the Bundi of Papua New Guinea (Zemel, 1989). The broad range in population averages for age at menarche will have some genetic basis, but is largely the result of ecological variation. The relatively late age at which girls from subsistence populations mature is therefore an indicator of the impact of their lifestyle, diet and behaviours on this process, just as girls in developed nations are impacted by the excesses they experience.

Given this evident variation in the timing of female maturation between disparate populations, coupled with evidence of a temporal shift in maturation schedules in western populations, the biomedical model of normal pubertal development discussed in the previous chapter doesn't seem sufficient to describe maturation across all ecologies. The model and timescale of puberty prescribed to by clinicians, which describes the typical ages of pubertal milestones, is clearly not globally representative and suggests that our understanding of "normal" puberty is limited to girls who grow up in developed, modern environments.

Our lifestyles within the modern built environment represent only a tiny percentage of human history. Populations that subsist on hunting and gathering, and agriculture, are similar to historical populations that make up a much greater proportion of that history. The tempo and timing of female pubertal development in response to the current ecological conditions of a subsistence

economy may be the closest comparison we have to understand what puberty may have looked like for girls before urbanisation and development, sanitation, and disease control. Moreover, by investigating the variation demonstrated across different populations that live – often in small and marginalised groups – traditional lifestyles, we might get a sense of what the limits of "normal" puberty look like in a more globally representative context.

Inter-population variation in female pubertal development

The evidence of population variation in female pubertal development is largely the result of James Tanner's work compiling data from populations across the globe in order to understand the limits of variation in age at menarche (see Eveleth and Tanner, 1990). While there is a known genetic component to female maturation (Kaprio et al., 1995; Ong et al., 2009a), Tanner and colleagues showed that varied environments produced significant phenotypic variation both in age at menarche and the maturation schedule of secondary sexual characteristics (Tanner 1962, 1981, Marshall and Tanner, 1969, Eveleth and Tanner 1991).

The differences between populations are understood because of developmental scales that categorise events in puberty, like the Tanner Scale described earlier in the previous chapter. The hegemonic model of biomedicine considers puberty relative to norms and pathology rather than from an adaptationist view of body-environment interactions. As such, western clinical medicine is concerned with the milestones of female pubertal development falling within pre-determined time slots of pubertal scales. However, this may be too prescriptive when considering variation on the population level. In order to understand the degree of variation among more disparate populations of humans, it is perhaps more beneficial to understand how lifestyle and environment may determine the onset and timing of those milestone events.

Life history theory: scheduling puberty

While biomedicine may tell us about the way puberty progresses and how the reproductive system matures, it could benefit from a theoretical framework that places pubertal development and other stages of growth in an evolutionary context.

The timing of pubertal onset and the re-initiation of the GnRH pulse can be considered within the framework of Life History Theory (LHT). LHT determines how finite resources in the environment are divided between the body's main processes of growth, maintenance and reproduction. The unique traits that result from those trade-offs characterise the life course and reproductive strategy of a species (see Charnov, 1991 and Stearns 1992). Pubertal onset is one such trait. In order to apportion energy to reproductive development and reproductive potential, energetic input into growth and maintenance must be reduced. Moreover, it must be reduced at a point when the energy trade-off would not negatively affect overall health or pose a risk of death. The timing of reproductive onset therefore balances the likelihood of current versus future (or potential) reproductive success given available resources (Ibid).

Earlier or later pubertal maturation determines the length of time during which an individual can undergo psychosocial development before they are fecund. The extended juvenile period is likely to have evolved in order to provision the individual for adulthood and offsets the high risk of juvenile mortality (Worthman, 1993). Females tend to mature around two years earlier than males (Tanner, 1962). Although early maturation offsets the risk of morbidity and mortality, unlike males, females also have the limiting pressure of menopause on reproduction. Earlier maturation maximises fitness by increasing the reproductively viable period. Males do not have the same limiting event on their reproductive life. While an extreme example, medical literatures has recorded that a man fathered a child when he was aged 94 years (Seymour et al., 1935).

As energy availability fluctuates, human females are capable of adapting to changes in environment and resource availability. Human ovarian function is sensitive to seasonality in food production, which affects both available food energy input during the hunger season, and energetic output in the form of labour and production during planting and harvesting seasons (Ellison, 1993; Jasienska and Ellison, 1993). Short-term changes in ovarian function ensure that maintaining fecundity in stressful environments does not compromise overall condition. The flexibility to direct energy elsewhere when times are tough, but invest when prospects improve, is an example of the important phenotypic plasticity associated with reproduction in risky environments. Thus, it follows that it would benefit the individual to delay the onset of pubertal development when their overall condition is poor. However, the determinants of normal ovarian function and the limits of plasticity in ovarian function are not necessarily equal to those that determine pubertal onset (Parent et al., 2003), although there are likely to be some similar mechanisms.

Responsiveness to the environment is reflected not only in the differences between individuals, but in variable *population* life history schedules that result from disparate ecologies. The timing of numerous life history variables like age at pubertal onset, age at first birth, inter-birth interval, and age at menarche, tend to vary between populations and indicate disease burden and energetic constraints, or lack thereof, as well as selection pressures (Lipson et al., 1993; Walker et al., 2006; Hochberg et al., 2011). Energetic constraint, i.e. immune compromise or malnutrition, will dictate pubertal onset and progression by producing trade-offs in energetic apportionment that increase input in growth and maintenance in times of energy paucity and reduce input into reproductive effort accordingly (Charnov, 1993; Stearns, 1992).

Given that the timing of pubertal onset should optimise reproductive potential, a degree of environmental responsiveness is of great benefit to the fitness of the individual. As such, it is important to recognise that puberty is *selected* to demonstrate a degree of plasticity (Worthman, 1993) and that describing

deviations from a prescribed model of "normal" as atypical pubertal development is not particularly helpful in uncertain or disparate environments because these deviations do not necessarily signal pathology. "Tracking" (e.g. Parent et al., 2003; Domine et al., 2006) of the environment increases the chances of reproductive success since the timing of, and degree of energy expended on the onset of reproductive function is dependent on an individual being able to detect whether an environment is favourable or not. Moreover, intra-population variation in pubertal timing reflects the responsiveness of individuals to the variations in the microenvironment (e.g. Anderson et al., 2003; Anderson and Must, 2005; Biro et al., 2006). The timing of puberty is therefore a life history variable that falls into a schedule of events – a life history strategy - that maximises fitness by determining when to make best use of available resources and producing trade-offs in energetic apportionment that increase input in growth and maintenance in times of energy paucity and reduce input into reproductive effort accordingly (Charnov, 1993; Stearns, 1992).

There are typically limits to the extremes of reproductive onset: that is, infants will not go through puberty simply if they are fat, and eventually even the smallest girls will begin pubertal development, but they are more likely to have poorer lifetime fitness and fertility scores than early-maturing girls. As a result chronic stress or seasonal stress may promote different maturation schedules. However, there have been a few examples of girls giving birth during early childhood. Lina Medina, a Peruvian girl who gave birth a few weeks after her *fifth* birthday, is the world's youngest known mother (Escomel, 1939). It was reported in 1939 that Lina had undergone precocious puberty (ibid). Lina's child was born by caesarean section and survived to middle age, and Lina was reportedly still alive in 2002 (Hamilton Spectator, 2002). This example of early motherhood demonstrates the physiological capacity of the female body to mature and reproduce in what are very, evolutionarily speaking, unfavourable conditions. But, it is likely that the child would have died without medical intervention because the young mother would most likely not have been anatomically developed enough to safely have a child by natural labour through the birth canal.

Data suggests that menarche appears to be earlier where life expectancy is longer as a result of better lifetime nutrition (Thomas et al., 2001). Early-maturing girls tend to have a fecundity advantage during all of their reproductive lives (Udry and Cliquet, 1982). However, paradoxically, girls who are in psychologically stressful or unfavourable environments where they are exposed to violence or instability (Belsky et al., 1991, Chisholm et al., 2005; Chilsholm and Coall, 2008), or insecure parental relationships (including father absence and partner or stepfather presence) (Draper and Harpending, 1982; Maestripieri et al., 2004) are also more likely to begin maturation faster than peers. Both of these effects contribute to the earlier age at maturation, and the lengthening of pre-menarcheal pubertal development, seen in developed nations, as well as the secular trend in age at maturation that was a response to improved living conditions with the advent of the industrial revolution in Europe and the West (Tanner et al., 1966). There is some concern that this change represents pathology (Christensen et al., 2010a, b), but it is also possible that it reflects a level of plasticity that has been a part of our evolutionary history and is only now evident in the phenotype. Examining the variation in maturation may provide more perspective on this.

Developing nations and the effect of urbanisation

Maturation is faster in developed countries (Bogin, 1999). Stearns and Koella (1986) note a reaction norm that girls who are undernourished will mature later at a lower height but there is no strict age or absolute height at menarche. However, there is variability in population means for age at menarche. Some of these population averages are changing as ecological conditions change. While the industrial revolution did not have equal impact for all populations, the effect of urbanisation is reaching increasing numbers of people in areas that were previously more isolated and used traditional modes of production.

Table 1.1 (Chapter one) shows the average age at menarche in a number of developed nations. Table 2.1 similarly shows population averages for pubertal

onset and age at menarche in a number of developing countries. It is evident that age at menarche is earlier in developed nations when compared with these developing countries. For example, none of the developed nations noted in Chapter 1 exhibit an age at menarche above 13 years, whereas among developing nations this is fairly typical.

Table 2.1 Pubertal maturation in developing nations. *median

Country	Year	Age at menarche	Age at B2	Age at PH2	Source	Country	Year	Age at menarche	Age at B2	Age at PH2	Source
Lithuania			10.02	11.20	Zukauskaite et al, 2005	Senegal			10.10*	10.30*	Jones et al., 2009
Chile (indigenous population)	Cohort 1990-1996	12.56	10.33*		Bustos et al., 2009	Sudan	2010	13.07			Aziem et al., 2011
Mexico	1998-1999	12.00*			Torres-Mejia et al, 2005	Zambia	1993	15.34	13.15		Gillett-Netting et al, 2004
							1993	14.53	11.47		
South Africa (Soweto)			10.20*	10.50*	Jones et al, 2009	Jamaica		12*	8.80*	9.90*	Boyne et al, 2010
Ethiopia	2007	14.80*			Zegeye et al, 2009	Egypt (Cairo)	1997	13.00*			Torres-Mejia et al, 2005
Kenya (urban)		12.50			Ogeng et al, 2011	Bangladesh (Matlab)	2001	2001	15.10*		Bosch et al., 2008
Malawi	1965-1994	15.10*			Glynn et al, 2010	Iran	2006	12.55	10.10	9.83	Rabbani et al 2010
Nigeria	1999	13.00*			Goon et al, 2010	China (Rural Han)	2005	12.92			Song et al., 2011
Igbo women	2005 (age	14.30			Umeora, and	India					

≤19)			Egwuatu, 2008	(Meghalaya)	2005-2006	13.22 12.13*	Deb, 2011
				(Bengal)	-	12.80 13.00*	Sanyal and Ray, 2008
Senegal	10.10*	10.30*	Jones et al., 2009	Indonesia (Jakarta)	1992-1995	12.89	Batubara et al, 2010
Lithuania	10.02	11.20	Zukauskaite et al, 2005	Nepal	2006	12.69 (mean)	Sunuwar et al, 2010

The accelerating effect of urbanisation on female pubertal development, and therefore overall life history strategy, can be seen in many developing countries that are rapidly experiencing environmental change. One such example is the marked difference in maturation rates between urban and rural black South African girls. Girls in an urban environment mature significantly younger than rural-dwelling girls (Cameron et al., 1990). The modern environment has also accelerated pubertal development at early breast stages in urban Kazakh girls. Urban girls were younger at breast stage 2 (B2) than rural girls. Interestingly the effect was not pronounced in later stages of breast development (Facchini et al., 2008). In China the ecological disparity between urban and rural is so pronounced that in 2005, despite China's strong position in world markets, mean age at menarche was significantly different at 12.92 for a rural population and 12.60 in an urban population (Song et al., 2011), suggesting that more rural populations are less influenced by economic development in China. It is also evident that under circumstances of migration and relocation from rural to urban environments (in this example, South Africa) girls grow taller and mature earlier than previous generations, despite their genetic predisposition to a particular maturation schedule (Walker et al., 2006). This might reflect an individual's capacity to better fulfil their genetic potential, which may have been possible for previous generations had they experienced similarly favourable conditions.

These changes in population averages in response to industrial and socio-political development are representative of the type of phenotypic plasticity that is important in ensuring that an individual's reproductive schedule is compatible with their environment. Life history strategies respond to changes in ecology in order to capitalise on increases in energy availability to improve reproductive fitness. It is likely that as more and more populations experience this transition they will be exposed to some of the same environmental pollutants and obesogens as industrialised nations, exposing them to increased risk of reproductive cancers and other co-morbidities known to be risk factors to well-nourished women with high baseline hormone profiles (Apter and Vihko, 1983; Eaton et al., 1994; Jasienska et al., 2000).

Chronic stress and puberty

Environmental or ecological shifts as illustrated above provide very tangible examples of the plasticity of the pubertal schedule and show us what puberty looks like under improved conditions as well as the detrimental impact of over-nutrition. However, it is difficult to understand whether the evident plasticity of puberty is a significant feature of our evolutionary history. While many studies of female pubertal development concentrate on the role of the environment in determining life history strategy, studies of such development, have been mostly limited to populations in developed or developing countries, and there are few longitudinal studies of female puberty among subsistence-level groups. Such data are immensely valuable since they provide a rare window into how human reproductive function responds to particular kinds of ecological stress reflecting conditions that are likely to have faced our human ancestors for much of our past. The timing of pubertal milestones is a good measure of resources and strategy since most is invested in somatic capital rather than inherited wealth and resources (Hochberg et al., 2011).

Subsistence-level populations give us the best understanding of how pre-demographic transition populations would have developed and maximised their reproductive fitness (Gawlik and Hochberg, 2012). By understanding the pubertal process under varying ecological conditions, and particularly under conditions similar to those experienced in our evolutionary history, it is possible to elucidate the ways that the process of pubertal development is mediated by environment and subsistence strategies. Moreover, it will improve understanding of the ways that *changes* in environment and subsistence strategies may impact pubertal development in females, particularly in the light of modern phenotypic change.

The slower maturation schedules that result from chronic food or immune stress, or seasonal stress provide girls with the opportunity to gain more in height and weight before investing their limited resources in pubertal onset,

although their adult body size is often smaller than population averages for well-nourished populations, who have been growing bigger and taller with improvements in sanitation, disease control and far less uncertainty in food availability than is typical in subsistence populations (Tanner, 1981).

Vitzthum (2001) proposes a model for understanding differences in population hormone profiles, and the ability of females to mature and ovulate with chronically low energy input. The Flexible response model (FRM) proposes that reproductive decisions are dependent on previous, or developmental, environments. Reproductive decisions are determined by absolute quality of conditions and also the relative quality of temporal conditions. If an individual is subject to relatively poor conditions during development and pre-adult stages then they are more resilient to adverse conditions. I.e. if you have been previously exposed to environments stressors you are better able to tolerate these conditions. Vitzthum uses this model to explain the relative ability of women in non-industrialised populations, with worse resources and periods of high labour intensity, to maintain a high fertility rate when the ovarian cycles of women in developed countries are easily disrupted by diet and exercise. Vitzthum states that this flexibility to adapt to stressful conditions has been shaped by natural selection (ibid). This model could be considered from a life history perspective in that developmental environments may set the trajectory for maturation, but the concept that chronic low energy throughout development increases tolerance to short-term insult has not been explicitly tested in human populations.

Moreover, it is not necessarily restriction in your own environment, but possibly your mother's environment that contributes to the set point of reproductive hormone production. Women who were exposed to the Dutch famine in 1944-45 did not necessarily have lower hormone profiles but they produced offspring who did (Lumey et al., 1995). In general though, these populations are still relatively well-off examples, and do not represent the extremes of groups who are exposed to chronically low energy levels (Nunez de la Mora and Bentley,

2008). Looking at individual subsistence populations will provide a better idea of the ways chronic stress affects the pubertal process.

Pubertal maturation and life history strategies in forager societies

When considering subsistence populations, much of the literature concentrates on traditional hunting and gathering, or forager, societies. Within hominin history, this also marks the traditional subsistence method of modern humans. Around 99% of our *Homo* ancestors' history is represented by the forager lifestyle (Gawlik and Hochberg, 2012). Forager subsistence typically, but not exclusively, relies on traditional gender roles whereby the men hunt for nutritionally dense meat sources. Women tend to be responsible for gathering berries, fruits and tubers depending on the local vegetation. Women's roles in forager societies also typically extend to cooking, childcare and other domestic chores. Forager girls begin to take on these roles in childhood. Therefore, forager girls are usually active and take part in some of their own provisioning, which in an environment of occasional food and immune stress, likely contributes to their relatively late maturation schedule compared with girls in developed countries who expend much less energy on self-provisioning during their childhood.

What then, do the immune compromises and food insecurity mean for the scheduling of pubertal development? Menarche occurs relatively late in foraging populations compared with ages in developed and developing countries (See table 2.2 overleaf).

The Hadza of Tanzania is one of the most intensively studied forager groups. Hadza girls reach menarche about 16-17 years of age. Status quo measures produce an average of 16.5 years. Median age at first birth is 19, which indicates an average two years of subfecundity since girls are typically engaged in sexual relationships soon after menarche (Marlowe, 2010). Compared with affluent and developed nations, food stress is higher among a population like the Hadza, but

they do not report one season as being harder than another, nor do they lose weight during the dry season (Ibid).

Table 2.2 Pubertal maturation and life history strategies in forager and subsistence, societies. *median

Population	Age at menarche (mean)	n=	Subsistence Pattern	Author
Hadza	16.5		Forager	Marlowe, 2010
Aeta	13.8	214	Forager	Walker et al., 2006
Agta	17.0		Forager	Goodman et al., 1985
Hiwi	12.6		Forager	Walker et al., 2006
Dobe !Kung	16.6		Forager	Howell, 1979
Pumé	13.0		Forager	Kramer et al., 2009
Gainj and Asai	18.4	104	Hunter-gatherers	Wood, 1980 in Walker et al., 2006
Bundi	17.2		Forager	Zemel and Jenkins, 1989
Dogon	16.7	588	Agriculturalists	Strassmann, unpublished data
Ache	14.0		Forager	Hill and Hurtado, 1996
Batak	14.6	36	Mixed	Walker et al., 2006
Tsimane	13.9	238	Farming-foraging	Walker et al., 2006
Wichi	12.9		Mixed	Walker et al., 2006
Sereer	13-14	343	Agro-pastoralist	Benefice et al., 1999
Kikuyu	15.9		Agro-pastoralist	Worthman, 1987

In a study of 24 savannah Turkana women, mean retrospective age at menarche was similar to the Hadza at 16.5 (Gray, 1994). Adolescent Turkana girls are known to experience moderate chronic food stress, despite evidence of positive energy balance in childhood (Galvin and Little in Little and Leslie, 1999). Similarly, studies of 51 Dobe !Kung girls in the Kalahari from 1963-1973 shows that menarcheal age fluctuated between 16 and 18 years of age, with an average around 16-17 (mean 16.6 years of age) (Howell, 1979).

The Bundi, with an average age of first menses at around 18 years of age, were believed to represent the upper limits of known natural menarcheal variation when they were studied in the 1960s (Malcolm, 1966). However, there is more recent evidence that shows menarche in rural Bundi populations has reduced to 17.2 years with a greater reliance on shop-bought foods containing higher fat and protein content compared with a traditional Bundi forager diet (Zemel and Jenkins, 1989).

Other forager populations have shown a steady decline in age at puberty. Probit analysis of menarcheal age among the Caboclo, who live along the Amazon River in Para, Brazil have shown a downward secular trend of around 0.24 years per decade between those born in 1930 to the current population- (Silva and Padez, 2006). This is likely due to some improvements to healthcare and better quality food, and access to state pensions, which benefit family units. Additionally, the Caboclo use some slash and burn agriculture, which is suited to low population density (Ibid).

The Ache have also experienced a downward secular trend due to their altered ecological circumstances. The change in age at menarche seems to appear in girls after first contact in 1960. Average age at menarche was 15.3 years in the forest, and 14 years of age when the population later moved to live on reservations (Hill and Hurtado, 1996). In 1987, comments were made that the trend had not

flattened out, and that girls born and raised on the reservations were experiencing their first menses before they showed any sign of pubic hair, which Ache women said had not been typical in the forest (ibid). In Tanner's model based on London girls this sequence of events is very unusual. Pubic hair development, like thelarche, typically begins early in puberty, and usually before menarche (Tanner, 1962). The sequence of events described for the Ache on the reservation could be a response to food security, particularly at birth, which might set the trajectory for age at menarche very early if energetic conditions for pregnant women and adolescent girls are relatively better than they had been in the forest.

Forager populations have to expend a greater amount of energy per individual in order to feed themselves. Although lots of societies traditionally work together and share larger or nutritionally valuable foods, the energy required no doubt affects the amount of energy that can be expended on reproductive effort while trying to maintain body weight and grow to adult size. There are greater energy trade-offs for forager societies than one would find in developed countries where food is readily available and food sourcing is no longer part of subsistence behaviour. LHT, as discussed in this chapter, incorporates reproductive strategy as part of an overall life history strategy in order to maximise reproductive fitness given energy and resource availability. While it appears that girls in developed and developing countries can mature early due to caloric excess, girls who are permanently energetically stressed also reach maturity albeit later. Just as human ovarian function is able to adapt to chronically low energy in order for women to conceive, so too do girls adapt to energetic conditions that are chronically low.

Growing larger is more likely to ensure that a woman has sufficient capacity to carry a child through pregnancy, as well as large enough pelvic dimensions to carry and give birth to a baby. As Ellison has discussed, skeletal maturity is a better predictor of menarcheal age than reaching a sufficient weight threshold (Ellison, 1981; 1982). A small pelvis may also account for higher risks of poor

birth outcomes among younger mothers if they mature while they still have child-like body shapes (Lancaster and Hamburg, 1986). Indeed, there is a high incidence of fistulas among young mothers in Sahelian populations, particularly where girls are malnourished and do not have the stature or physical capacity to give birth without damaging their genitourinary system (Wall et al., 2004). Fistulas that damage the perineum and open up a tract between the vagina and the rectum can often result in lifelong incontinence (particularly where medical intervention to repair the fistula is unavailable), pain during intercourse, and detriments to future fertility, and thereby social stigma (Wall et al., 2004). The pelvis of some younger mothers is so small that the head of the baby puts pressure on the maternal pelvic bone, causing tissue necrosis. The dead tissue can then slip away causing the fistula (Van Beekhuizen et al., 2006). Often, the pressure on the neonate's skull is so great it can result in foetal death (ibid).

A long period in which to learn skills could be a serendipitous advantage of delayed maturation. In a test where girls and boys were compared based on time in school versus time spent practising hunting, gathering and food processing activities, there was no convincing evidence that practise improved productivity in a forager population. Extra years digging tubers for girls and extra time practising archery skills for boys does not increase productivity and success when compared with peers who have not had as much practise at these skills. It seems that of great importance is the opportunity to increase productivity by increasing size and strength over time (Blurton-Jones and Marlowe, 2002). Bogin (1999) suggests that mid-childhood may be a time for acquiring skills. Marlowe (1997) also suggests that practising skills in the teenage years is a good opportunity to display skill and develop a reputation (Blurton-Jones and Marlowe, 2002). The ability to increase productivity is invaluable in the reproductive years since an individual is able to provision themselves and their offspring once they have become physically capable of having children.

The Aeta from Luzon, Phillippines are a nomadic population that live an increasingly marginalised existence in mountainous regions. Menarche occurs at

an average age of 13.8 years (Walker et al., 2006). The Aeta are recognised to be in transition as the result of deforestation in their traditional home range, and evidence from a previous study of a closely related population, the Agta, found mean menarcheal age to be 17.0 years around 1980 (Goodman et al., 1985). This reduction in age at menarche may be the result of the adoption of subsistence methods other than traditional hunting and gathering, and the effect of urbanisation. As the Aeta transition from their traditional lifestyle to more settled groups as the result of deforestation and mining they may be forced to live on a different diet, or make use of crops that provide more food security than their traditional diet.

What might a move away from hunting and gathering mean for female pubertal reproduction? Relative to a reliance on agriculture, foraging is protective against disease transmission and improves health. Although there was an increase in reproductive success with the demographic and agricultural transition, there is a decrease in health associated with the adoption of agriculture due to increased population density, increased workload, food crises, and contact with cattle (Froment, 2001). Despite the risk of famine and poor crops, agriculture does generally provide greater food security overall. We should see earlier maturation in subsistence farmers because increased population density increases competition for food and resources and the likelihood of communicable disease (ibid). There is also evidence that total fertility is higher for intensive agriculturalists compared with all other subsistence ecologies (Bentley et al., 1993), which indicates the potential for improved conditions that could also support earlier maturation. Indeed, the transition in subsistence methods experienced by the Aeta may be responsible for their relatively early age at menarche among foragers, as outlined above.

Fast life histories: The savannah Pumé and the Hiwi

Not all non-western populations mature later. Pumé and Hiwi girls both have very early age at menarche in the subsistence paradigm. The Hiwi live in small bands in Venezuela and Colombia, and subsist mostly on water mammals and

gathered fruits and roots (Hill et al., 2007). Average age at menarche for Hiwi girls is 12.6 (Walker et al., 2006). However, Hiwi have a very long period to first birth -- around 6.5-7 years compared with 2.6 years for the Pumé (Walker et al., 2006; Hochberg et al., 2011).

Savannah Pumé girls demonstrate very fast life histories, with average age at menarche comparable to Western Europe and North America at 12.96 (Kramer et al., 2009). No girl over the age of 14 is pre-menarcheal and there is only an average of 2.6 years between menarche and first birth despite such a young age at menarche. The Pumé are mobile foragers living between river systems. This lifestyle produces many energetic trade-offs as the result of high disease burden, immune costs and high mortality risk. It is suggested that Pumé foragers have evolved a system of early maturation in order to offset those costs associated with their risky environment (ibid).

The similar savannah environment of Hiwi and Pumé foragers, and therefore nutritional constraints, as well as similar subsistence patterns suggest, that differences in their maturation schedule may be cultural rather than strictly biological (Kramer and Lancaster, 2010). Since both populations have no access to contraception this might represent either a longer period of sub fecundity among the Hiwi, or underlying cultural norms that dictate an optimal timing for first births. Hunter-gatherers classically have a long period of subfecundity following a late menarche (Lancaster in Lancaster and Hamburg, 1986).

Despite the risks associated with early age at first birth, i.e., higher percentage of spontaneous abortion, low birth weight etc. (Lancaster and Hamburg, 1986), and fistulas (Wall et al., 2004; Van Beekhuizen et al., 2006) there seems to be no fitness advantage to delaying first reproduction for savannah Pumé foragers, even though 14 year-old girls are significantly more likely to lose their first born child than 17 year-old girls (Kramer et al., 2009). Presumably this is mitigated by the extra opportunities to reproduce by beginning reproduction at 14 rather

than 17. The Pumé begin sexual contact soon after menarche, but this may not be the case for the Hiwi.

Most subsistence level populations, and certainly historic European populations where nutritional intake was lower than today, show a later relative age at menarche and pubertal onset. Using a life history perspective, reproductive ecologists have generally agreed that energetic constraints involve trade-offs between growth, maintenance and reproduction leading to delayed reproductive development where resources are limited. How then is it possible for girls to reproduce earlier when they themselves are under energetic stress?

High immune costs associated with poor environment and high childhood morbidity paradoxically predict earlier maturation for both Pumé and Hiwi girls. Despite the high burden on immunity, Pumé and Hiwi girls still invest their energy into early maturation. However, the Pumé are especially unique in that they are able, despite their young age and small size, to reproduce at such a young age, where the effort of early maturation does not produce a significant trade-off to delay first reproduction. This unique strategy may be explained by the availability of pooled energy budgets, which buffer reproductive capacity against immune insults (Kramer et al., 2009; Sharrock et al., 2009), as opposed to a bound-energy model, whereby the individual is bound by the provision of energy from their own metabolic budget.

While Pumé girls have the majority of their height gains before menarche, they are only around 50% of their adult weight at 10. They also continue to grow after first birth (Kramer et al., 2009). Pooled energy budgets (the pooled contribution of energy from members of a group) continue to support an individual while she reaches her full height potential and continues to gain weight (ibid), which likely provides the extra energy necessary to produce a child when others would be under significantly greater growth constraints. Although Pumé girls are very likely to lose their first child, and even though their weight increases and risk of infant death reduces with time there are no fitness gains to delaying maturation

(Kramer et al., 2009). This is perhaps due to early maturers having short periods of sub fecundity, or simply because they have more years over which to reproduce to mitigate the effect of early child loss on lifetime fertility.

The pooled energy budget may be one explanation for fast life histories in compromising environments. However, even though food is preferentially shared with young mothers (Kramer and Greaves, 2007), girls must be further buffered against food insecurity, somehow, since many other subsistence populations food share and they do not exhibit this very unique pattern of very early maturation and very early first birth. The Pumé represent an extreme in reproductive plasticity and much more work will be required to elucidate the factors that could provide greater energetic buffering to Pumé girls compared with similarly challenged populations.

The Pumé might also stimulate a greater focus on the role of skeletal maturation on pubertal development. Ellison (1981) found that height, rather than a threshold weight was more associated with age at menarche. Ellison (1982) also highlighted the physiological importance of skeletal maturation at puberty since sufficient pelvic growth and dimensions are imperative for a woman to give birth without risk to herself or her baby. Kramer et al (2009) state that girls have gained most of their height, but not weight by age 10, which lends itself to the theory that their early skeletal development is associated with their fast life history strategy. Indeed, early-maturing girls in developed populations are often taller than their later-maturing peers when they begin puberty (He and Karlberg, 2001). While pooled energy budgets might be the mechanism that supports early age at first birth for early-maturing Pumé foragers, the factors or context that elicit pre-adolescent height growth might be the key to understanding this unique, very fast life history.

Pubertal maturation and life history strategies in agricultural and pastoralist societies

As outlined above, the introduction of agriculture is associated with greater food security, even accounting for periods of famine and crop failure. The effect of a crop from a reliable, regular harvest, or meat from a grazing herd, probably supplemented with other foods, is demonstrated in the relatively earlier age at puberty for girls who live in agro-pastoralist communities compared with forager bands (see table 2.2). The greater availability of food and the reduction in time spend gathering and picking foods compared with foragers contributes to fewer trade-offs in energy output, thereby supporting the energetic costs of pubertal onset at an earlier age.

While pastoralism and agriculture are relatively more recent modes of production in human history compared with hunting and foraging, the physiological response of females to this change demonstrates the capacity of female reproductive system to respond to new ecological conditions. Moreover, it highlights that the degree of plasticity in female pubertal onset in response to newer environments, including urbanisation, may be operating within degrees of variation that have been exhibited during our history in response to historical ecological shifts.

Age at menarche has been retrospectively studied among the Kipsigis, an agro-pastoralist group of the Rift Valley region, Kenya. Kipsigis herd cattle and grow maize and wheat as well as cultivate vegetables (Borgerhoff Mulder, 1989). Age at menarche was established by questioning women on the timing of their clitoridectomy ceremony, which follows in the first December after menarche. Other women in the community confirmed age at menarche, in relation to other notable events, to establish a firm chronology for each individual. Mean estimated menarcheal age was 14.9 (range 12-19) (ibid), which is much younger than other agro-pastoralist groups (see table 2.2). Age at menarche is based on mean age at clitoridectomy minus 0.5 years, under the assumption that any girl

undergoing clitoridectomy in December is equally likely to have had menarche at any point in the preceding twelve months (Borgerhoff Mulder, 1989).

A multi cross-sectional study of 343 agro-pastoralist Sereer girls aged 0-5 from Niakhar district in Senegal were examined in 1983-4 and again as adolescents aged 12.5-14.5 in 1995 (Benefice et al., 1999). Menarche and Tanner breast stage were recorded in the girls who were either 13 or 14 years old. Sereer girls were both lighter and shorter than African urban reference populations (Benefice et al., 1999). Over a third (39%) of girls aged 13, and almost a quarter (24%) of girls aged 14, were pre-pubertal; only 5 girls were menarcheal (ibid).

Data of menarcheal age in girls from other mixed economy and agriculture-based societies shows that girls experience menarche between 13 and 14 years of age (See table 5.3). However, girls in the Dogon, who rely mostly on millet farming, seem to mature much later than these mixed economy groups. Although the Dogon do keep some livestock like goats (Strassmann, 1997), agriculture is their main provision for subsistence (Strassmann, personal communication). Median age at menarche is 16.7 years of age for this population (Strassman, unpublished data).

The Dogon organise their subsistence patterns using economic units called "work-eat groups" made up of men, women and children who farm a particular area of millet. Although not analogous to family units, husbands and wives belong to the same work-eat groups, and these are a woman's only access to wealth. The work-eat group determines the standard of living for all of its members and therefore determines nutritional status and fecundability for women (Ibid). Perhaps a greater reliance on one particular food source, or one system or provision -either foraging or agriculture, which both have their risks of high energy expenditure and crop failure respectively - over a mixed-economy subsistence pattern is more energy-restrictive, or s not so protective against food insecurity.

Age at menarche varies among similar subsistence level groups. For example, during a 2-year mixed longitudinal study the Kikuyu - a Bantu-speaking agriculturalist population from the central highlands of Kenya - were found to have a median age at menarche of 15.9, (range 10.5-17) (Worthman, 1987).

The pubertal process and Tanner stages among subsistence populations

Marshall and Tanner (1969) described typical pubertal stages and times for transition between those stages in English girls as described in Chapter 1, and there is evidence that some populations differ from this norm, although data on age at thelarche, pubarche or indeed any indication of how quickly or slowly girls might progress through the stages of breast and pubic hair development is scarce.

One example of known pubertal tempo comes from the Kikuyu of highland Kenya, who begin puberty around 3 years later than North American (Anderson et al., 2005) and UK girls (Christensen et al., 2010), and also take, on average, 2.9 years from Tanner Breast Stage 2 to menarche (Worthman, 1987), slightly longer than the 2.3 years described in the English girls by Marshall and Tanner (1969). This demonstrates the capacity for plasticity in the onset of female pubertal development and the process of puberty. It also highlights the role of differing ecologies in eliciting a reproductive strategy that might differ considerably between populations. While there is concern that the length of puberty (the time between pubertal onset and menarche) is extending in the UK (Christensen et al., 2010a; 2010b), these data serves to highlight the presence of a similar pubertal strategy in a far-removed population who are not so well nourished and do not have the same environmental exposures to endocrine disruptors or to prolonged food abundance.

In other aspects of puberty, the Kikuyu seem to follow the “norm”: hormonal shifts in girls are in line with the pattern seen in Western populations where

oestradiol rises with initial breast development and the development of the ovaries follows a rise in luteinising hormone (LH) (Worthman, 1987). While girls in the UK may begin puberty much younger as the result of calorific excess and positive energy balance, as well as exposure to endocrine disrupting xenoestrogens, they are beginning to exhibit strategies associated with a population under very different energetic conditions. The Kikuyu provide an excellent example of the extent of plasticity in female pubertal development that would otherwise cause concern in the context of biomedicine, but is demonstrably "normal" under these circumstances.

This Chapter has explored the variation known in modern subsistence populations and demonstrates the known, expected accelerating effect of a change to a new ecological circumstance on pubertal development, whether that is between traditional modes of production, or in response to urbanisation and development. The evident degree of plasticity in the timing and tempo of female pubertal development in response to various ecologies also suggests that pubertal development is selected to be variable, most likely as the result of ecological variation throughout human history. The western biomedical model of "normal" pubertal development must therefore be considered within its own context, and is not a suitable measure of the timing and tempo of the pubertal process in all populations.

In the modern western environment girls are now exposed to manmade chemicals and pollutants that are entirely novel in all of human history, and are capable of blocking or mimicking the actions of endogenous oestrogens. The introduction of these chemicals has happened over the last half century and likely represents one of the most extreme challenges to female reproductive ecology in all of human history. How has female pubertal development responded to the introduction of these chemicals, which are capable of interfering directly with the function of endogenous steroid hormones? The following chapter will explore both the effects of manmade chemical pollutants on female pubertal development, and consider to what degree these compounds

may be responsible for accelerating pubertal development in urban, developed populations.

Chapter Three: Endocrine disrupting chemicals and accelerated pubertal development

This chapter explores the effects of xenoestrogenic compounds and other endocrine disrupting chemicals (EDCs) on health outcomes, and, more specifically, their possible effects on female pubertal development. As discussed in Chapter one, there is evidence for a continued secular trend in age at menarche, but more significantly, evidence of acceleration in the age at pubertal onset, which may not be entirely explained by the concurrent trend for overweight and obesity among children. There is a building body of literature that suggests xenoestrogens and other synthetic compounds, which were introduced into our environment through industry in the mid-twentieth century, may contribute to accelerated pubertal onset by mimicking or blocking the actions of endogenous steroid hormones. Additionally, EDCs have been shown to affect weight status, which may exacerbate any effects overweight may already have on female pubertal development, and may also confound the effects of positive energy balance.

Box 2

Endocrine disrupting chemicals (EDCs)

An endocrine disrupting substance is a compound, either natural or synthetic, which, through environmental or inappropriate developmental exposures, alters the hormonal and homeostatic systems that enable the organism to communicate with and respond to its environment (Diamanti-Kandarakis, 2009).

Direct evidence of the influence of EDCs on human female reproductive maturation is, as yet, both limited and inconclusive. However, the increasing production and use of these anthropogenic compounds correlates with both the secular trend for earlier female maturation, and the trend for increased

overweight and obesity, which may represent a network of relationships between these factors. The purpose of this Chapter is to discuss the actions of EDCs in humans and the potential effects of EDCs on accelerated pubertal onset.

What are endocrine disruptors?

An endocrine disrupting substance is a compound, either natural or synthetic, which, through environmental or inappropriate developmental exposures, alters the hormonal and homeostatic systems that enable the organism to communicate with and respond to its environment (Diamanti-Kandarakis, 2009). Broadly, they contain halogen group substitutions by chlorine and bromine (ibid), and have characteristics that mimic natural steroid hormones and allow them to act as agonists or antagonists, minimising or blocking a cellular response (Sharara et al. 1998). These mimics can derail an animal's development, permanently distorting its reproductive, immune, and neurological systems (Dold, 1996).

The endocrine system maintains the function of many of our key systems by overseeing and relaying signals internally, that may or may not be augmented by our environment. These signals are hormones, which act as messengers on an organic, tissue, and cellular level, telling each tissue what to do and when to do it (Dold, 1996; Ellison, 2009). During foetal development this process is even more delicate as hormones tell our body's first cells what to become during differentiation, down to determining the sex of an individual in response to genetic programming. Even more importantly for the life course this process also determines how our bodies will respond to external stimuli, i.e. our ecology (Dold, 1996).

Rachel Carson's seminal work on environmentalism, Silent Spring, spelled out the devastating impact of chemical pesticides on our landscape, and spawned a generation of researchers dedicated to understanding the true impact of chemical toxins on our own species. In the second half of the twentieth century, research into strange instances of localised animal population bottlenecks, and reproductive abnormalities, came to light. Many of the chemical pesticides and

industrial materials these animals had come into contact with were acting as endocrine disruptors capable of mimicking or blocking the effects of endogenous hormones.

Figure 3.1 shows the chemical structure of some of the most ubiquitous EDCs. As is illustrated, common to all of these compounds is the benzene ring structure, which is also found in endogenous oestradiol.

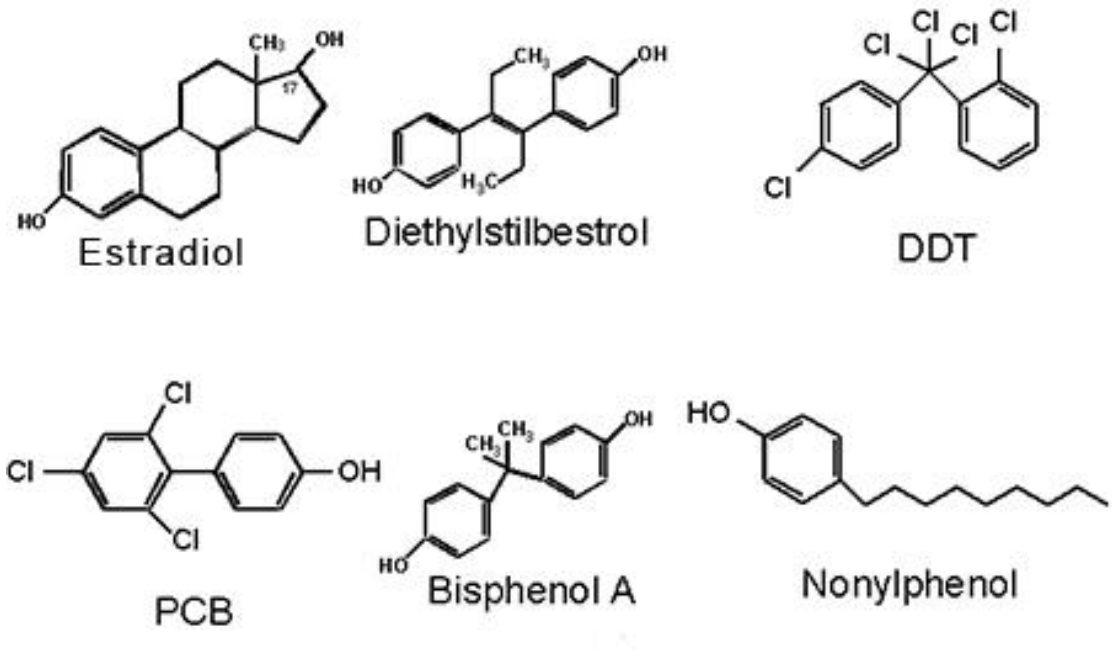

Fig. 3.1 EDC structures from www.sccwrp.org

EDCs include xenoestrogens, which are synthetic compounds that have oestrogenic effects; obesogens, which can alter fat storage and metabolism; and phytoestrogens, which are natural plant oestrogens. EDCs are sometimes referred to as persistent organic pollutants (POPs) since their chemical structures are resistant to degradation and remain in the environment for very long periods. Although the chemical structure of EDCs is not identical to endogenous oestrogen they contain the benzene ring found in oestrogen, which allows many of these chemicals to interact with oestrogen receptors thereby stimulating or blocking their action (Colborn et al., 1996). Although EDCs may

not have the same affinity for the receptor as endogenous steroids, they can still promote a strong positive response.

Animal studies

A number of animal studies throughout the twentieth century found evidence of reproductive abnormalities and dysfunction that could be explained by contact with various endocrine-disrupting chemicals. From the late 1930s into the 1950s Charles Broley studied the American bald eagle by annually banding eaglets. Broley noted sterility and bizarre mating behaviour among nesting pairs (Broley, 1947), which were later attributed to DDT (dichlorodiphenyltrichloroethane) exposure (Wiemeyer et al., 1993). DDT was originally produced as a powder disinfectant for the military, but was more commonly used as an insecticide in areas of high malaria incidence. It is banned across Europe, but is still widely used in areas where the burden of malaria is believed to be of greater concern than the possible negative health outcomes associated with its use.

These findings were followed by evidence of a drop in otter populations during the 1950s (Chanin and Jefferies, 1978), and a similar drop in mink populations around the Great Lakes of America during the 1960s in response to polychlorinatedbiphenyl (PCB) exposure (Auerlich *et al.,* 1973; Jensen et al., 1977). Thinning gulls' eggs in Southern California during the 1970s (Fry and Toone, 1981), and the low frequency of alligator eggs hatching in already small clutches in Lake Apopka, Florida in the 1980s (Guillette et al., 1994) were both attributed to chemical exposure, the former from a chemical spill that included DDT.

Further deleterious effects of endocrine disruptors in animals include reproductive failure in the common seal *Phoca* in response to PCB pollution in the western river Rhine (Reijnders, 1986), and a variety of reproductive abnormalities in Dall's porpoises (Subramanien et al., 1987), rainbow trout

(Jobling et al., 1996), and juvenile alligators (Guilette et al., 1994) all in response to contact with substances we now recognise as endocrine disruptors.

Not only might these exogenous chemicals disrupt the delicate balance of endogenous reproductive hormones throughout reproductive life, they could have far more profound effects at an early stage by upsetting the precision process of sex determination. Frederick vom Saal highlighted the effects of varying steroid hormone exposure in the womb in a mouse model and found deviant, aggressive females; and males presenting with lordosis, the sexual position typically adopted by females, which angles the pelvis anteriorly (vom Saal and Bronson, 1980). If hormonal insult occurred in humans as the result of endocrine disruption during early fetal development it could realise media fears about feminised boys, and a merging or distortion of sexual differences could lead to infertility in the most extreme cases.

Evidence from animal models does not prove the risk or safety to humans. The evidence of endocrine disruption and the effects on reproductive function in animals is convincing and numerous, but it is imperative to carry out research among human populations in order to understand exactly how, or if, synthetic compounds are altering human physiology.

Route of action in humans

The first example of endocrine disruption in adult women occurred 40 years ago when a very rare form of vaginal cancer was found at increased levels in young women born to mothers treated with the potent synthetic oestrogen diethylbesterol (DES) during pregnancy (Herbst et al., 1971). These women have since been given the moniker “DES daughters” (Bell, 2009). Doctors Herbst and Scully documented the cases of 7 young Caucasian women who had presented with startlingly similar symptoms of irregular long-term menstrual bleeding. They were treated with oestrogens, yet the problems persisted. Upon examination all were found to have an extremely rare form of adenocarcinoma,

which is not normally seen in women less than 50 years of age. One girl had an endometrial form, the others clear cell form. Not only was it odd that these women were so young, but also that a cluster of patients could be experiencing such a rare disease. Some were treated with radical surgery to remove their uterus and vagina, depending on the extent of the cancer, others had only the tumour removed, and one was so advanced she survived only five months after diagnosis (Herbst and Scully, 1970).

It was eventually revealed that all of these girls were exposed to the drug, diethylstilbestrol (DES) *in utero* from the first trimester onwards (Herbst et al., 1971). DES was offered as a wonder drug to protect against miscarriage and "difficult pregnancies". It is now understood that the ability of DES to stimulate this rare cancer is due to its bioavailability since it does not bind to blood proteins (Colborn et al., 1996).

Another decade later the greater realisation of the overwhelming threat posed by anthropogenic compounds really came to light. As Colborn et al. put it:

> For years, the ongoing discussion about possible human health risks from synthetic chemicals has been based on the assumption that most human exposure comes from chemical residues, primarily pesticides, in food and water. Now Soto and Sonnenschein had discovered hormone-disrupting chemicals where you would least expect them- in ubiquitous products considered benign and inert (Colborn et al., 1996).

This passage refers to the accidental discovery by Soto and Sonnenschein that the plastic tubing they had been using as part of a study of cell proliferation in oestrogen-sensitive breast cancer cells, were in fact having a positive effect; the plastic was leaching the xenoestrogenic compound p-nonylphenol and causing abundant cell growth. The levels of oestrogen-like substance involved were so negligible it was hard to conceive that it had such an obvious, visible effect (Soto and Sonnenschein, 1983; 1984).

At around the same a Spanish reseach laboratory was looking at the levels of oestrogen mimics leaching from food packaging, like the lining of tins. What they

discovered was that these so-called weak oestrogens were found in extremely high levels in food packaging (Brotons et al., 1995). In the light of work like that of Soto and Sonnenschein, Brotons et al. were convinced this required greater attention. Soon a team at Stanford found evidence of leaching of Bisphenol A BPA into distilled water from polycarbonate flasks after autoclaving (Krishnan et al., 1993). This not only has ramifications for laboratory procedures, particularly relating to oestrogen-sensitive compounds, but also with regard to the effects of heating plastics in our everyday activities. More recently the effect of BPA leaching into plastics has been linked to babies bottles when they are heated during sterilisation (Aschberger et al., 2010).

The implications of this finding were both startling and far-reaching. Gradually, more and more evidence came to light of the extensive effects of EDCs on human health outcomes. Table 3.1 (overleaf) describes the effects in humans of some of the most common EDCs found in environments across the globe. So many of them are found in everyday products like tins, plastics, cosmetics etc., and enter the body both through the diet and dermal application (Colborn et al., 1996). Much of the knowledge on EDCs is the result of severe contamination incidents localised to particular populations that suffered the burden of the lasting detrimental effects on health.

For example, PCBs are thought to be the most stable of the xenoestrogenic compounds (Fein et al., 1984). One of the most widely-reported exposure incidents of PCBs was the exposure of a community in Taiwan to cooking oil containing thermally degraded PCBs. It contained dibenzofurans (entirely synthetic), which are even more toxic than PCB itself. The implications of the contamination were widespread among the affected community. Poor birth outcomes and life-long problems with bronchitis, eye-swellings and conjunctivitis occurred, as well as hyperpigmentation, chloroacne, reduced weight and height in babies born who were either *in utero* during the exposure, or conceived following the contamination (Rogan et al., 1988).

Table 3.1 Common endocrine disrupting compounds

Chemical/Element	Common use	Target	Effect	Notes
Diethylstilbestrol (DES)	Pregnancy aid[1]	Genital tract		Cancers of the uterus and vagina[1]
Dichlorodiphenyltrichloroethane (DDT)	Organochlorine insecticide[2]	Adipose tissue	oestrogen agonist and an androgen antagonist	Evidence of pregnancy loss and high pre-term birth may be confounded by poor local water quality[2]
Dichlorodiphenyldichloroethylene (DDE)	Metabolite of DDT, often leached into riverine systems[3]	Adipose tissue	Oestrogen mimicker and blocker	Extremely stable with a much longer half-life than its source[3, 15]
Polychlorinated biphenyls (PCBs) and dibenzofurans	Oils , used in chlorinating and bleaching paper[12]	Adipose tissue, breast, cranium	Oestrogen mimicker and blocker	Possibly capable of delaying breast development[3] Found to reduce head circumference in babies born to mothers who ate Lake Michigan fish contaminated with levels PCBs considered normally dietary exposures[4] Poor birth outcomes, long-term problems with bronchitis, eye swellings and conjunctivitis, hyperpigmentation, chloroacne and reduced height and weight all associated with babies born who were either exposed *in utero* or conceived following parental exposure to debgraded PCBs[5] Considered the most stable persistent organic pollutant[6]
Polybrominated biphenyl (PBB) including dioxins	Flame retardant[13]	Adipose tissue	Competitive oestrogen inhibitor	Associated with earlier menarche in girls exposed *in utero* and postnatally, particularly among those who were breastfed[7]
Bisphenol A (BPA)	Originally a synthetic oestrogen. Used as a plasticiser, polycarbonate plastics, epoxy resins to line cans[2]	Endometrial endothelial cells	Oestrogen blocker	Responsible for increased cell proliferation and increased cell death in the endometrial endothelial cells[8] High concentrations associated with PCOS and obesity[8]

Phthalates	Plasticiser found in toys, cosmetics, pharmaceuticals, medical tubing[2]	Adipose tissue	Oestrogen mimic/androgen antagonist	Levels found in urine indicative of household exposure. They become harmful upon leaching contact or heating, which releases particles into the atmosphere[9,14]
Atrazine	Crop spray[10]	Breast/foetus		Inreases risk of breast cancer and the risk of pre-term birth[10]
Zeranol	Growth promoter for livestock[10]	Breast		Increased risk of breast cancer[10]
Parabens	Cosmetics[11]			Direct contact with the breast and underarm area avoids metabolism and could therefore promote breast cancer[11]
Lead	Heavy metal			
Aluminium	Metal, incredient in deodorant[11]			Direct contact with the breast and underarm area avoids metabolism and could therefore promote breast cancer[11]
Phytoestrogens/ lignans/isoflavonoids	Naturally-occurring plant oestrogens[5]			Foetal issues, skin conditions (hyperpigmentation)[2]

[1]Bell et al., 2009; [2]Patisaul and Adewale, 2009; [3]Wolff et al., 2008; [4]Fein et al., 1984; [5]Rogan et al., 1988; [6]Loganathan et al., 1993; [7]Blanck; [8]Bredhult et al., 2009; [9]Swan, 2008; [10]McLachlan et al., 2006; [11]Darbre, 2006; [12]Schoeters et al. 2007; [13]Roy et al., 2009; [14]Autian, 1973; [15]van Hove Holdrinet et al., 1977.

PCBs were originally produced for use in electricity transformers since they were non-inflammable. As with many xenoestrogens that were produced for industry this became their lasting problem: persistence (Colborn et al., 1996). On a global scale PCB risk is greater than that of DDT since DDT burdens have reduced in humans thanks in large part to global policy on its use and risk (Loganathan et al., 1994)

A decline in the use of organochlorines in riverine systems has seen their concentrations decrease significantly (Loganathan et al., 1994). Concentrations increase in coastal seas and closed water systems, with a highest rate in open

oceans, which act as a “sink” or end-point for these compounds. It is difficult to eliminate these compounds completely given their stability and persistence in water systems (ibid).

Phthalates, a component of epoxy resins used to line tins, are also found in household products like cosmetics and baby lotions, pharmaceuticals, and toys (Patisaul and Adewale, 2009; Roy et al., 2009). The risk to infants is increased since the dose in products is relatively high for a small baby compared to the effect it would have on an adult (Sathyanarayana, 2008). Phthalates become harmful to humans upon leaching contact, or heating to release particles into the local atmosphere (Autian 1973). Their use in so many household items and products makes the potential for contamination ubiquitous. BPA is equally abundant in households. It is found in babies’ bottles, tableware, plastic linings of food tins, and dental fillings (Bredhult, 2009). Parenting forums and websites are concerned with infant exposure to BPAs from bottles and dummies (baby.families.com; www.parenting.com).

Despite the health risks associated with DDT use (see table 3.1) it is seen as the lesser of two evils in areas where malaria kills, and there is also debate that complications associated with DDT-like high rate of preterm birth, and pregnancy loss- can be confounded by poor local water quality and inadequate nutrition (Patisaul and Adewale, 2009). Dichlorodiphenyldichloroethylene (DDE), the main metabolite of DDT, is more persistent still than DDT. Along with the understanding that DDT is recognised as an oestrogen agonist and an androgen antagonist, DDT shows the potential for EDCs to have multiple mechanisms of action and pose a lengthy threat to health after initial use (Patisaul and Adewale, 2009).

Xenoestrogens from everyday products like plastics and cosmetics leach from their source and eventually end up on air currents and in water systems. One tiny molecule can be taken up by algae or a similar water-bound life form and stored within its cells. At this point it has entered the food chain. Small fish,

followed by larger fish, small sea mammals, larger sea mammals and eventually large land mammals and humans prey on the previous in turn. As each larger species consumes the smaller there is significant bioaccumulation of endocrine disruptors since eating many prey with a low level of contamination results in a larger burden in the predator species (Colborn *et al.,* 1996). This kind of bioaccumulation is a simplified model, but results in human exposure to various chemicals.

Other routes of contamination: crossing the placental barrier and breastfeeding

It is now well documented that endocrine disruptors can be passed to infants through both the placental barrier and during breastfeeding (Dewailly et al., 1989). Some of the effects seen in adulthood, like reproductive cancers, may be the result of exposures passed to infants this way. In one investigation in newborns, transplacental exposure to PCBs resulted in poorer Bayley scores relative to controls, in the form of reduced psychomotor scores (Gladen et al., 1988). Bayley scores are a measure on the Bayley Scales of Infant Development that indicate motor, language and cognitive development of infants (Lowe et al., 2012). This mechanism could have detrimental consequences for any number of developmental processes both *in utero* and during childhood (Gladen et al., 1988). Other evidence includes phthalates found in amniotic fluid, which is evidence of passage across the placenta (Tsutsumi, 2005). Moreover, PCBs and dioxins are capable of affecting trophoblasts and thereby placental development and function (Fowler et al., 2012).

The timing of an endocrine insult *in utero* may determine its effect. Of particular importance are periods of organogenesis, where developing structures will be especially vulnerable; the same agent administered at a different stage may have an entirely different effect on the growing foetus or indeed later in life (Agency for toxic substance and disease registry, 1993). Additionally, duration and type of contaminant would alter the developmental response (Field et al., 1990; Sharara et al., 1998). There is no knowing what the effects are of an insult that

occurs at different points throughout gestation: first, whether they have immediate impacts on the developing foetus, and secondly on their potential to result in altered postnatal development or even adverse health outcomes in adulthood.

The risk to newborns is contamination via breast milk. The lipophilic nature of EDC means that lactation is the greatest route of excretion of endocrine disruptors in women as fat stores are mobilised to provide for the nursing infant. They migrate to the breast and then become stored in the infant fat tissue after ingestion. In a Sudanese population, women were found to be excreting aflatoxins in breast milk that would be considered unsafe for human consumption if detected in animal milk (Coulter et al., 1984). Hepatic or other routes of excretion are so minimal that as a nursing infant stores these chemical residues of nursing they will have relative EDC levels far above that of the mother. The infant acts as a sink for the chemicals excreted by the mother and they are likely to keep those initial doses throughout their lifetime. The effect can only be diluted with growth as the relative concentration in the body decreases (Alstrup and Slorach, 1991).

The initial dose of disruptors is not the same for all infants; it depends on a number of factors. Body fat is in equilibrium with blood fat, and so this would determine how much is mobilised to the breast (Samogyi and Beck, 1993). Additionally for the infant, the length of feed, time of day, and whether it is the beginning or the end of the feed can affect the concentration of EDCs in the milk (Slorach and Vaz, 1985). Individual compounds also behave differently to one another, and differently again as a mixture; their molecular weight, pH, binding properties and polarity will all affect their affinity for storage and persistence (Samogyi and Beck, 1993). This is important in considering ways of controlling infant exposure to xenoestrogens, and similarly continued contamination of mothers, since both mother and infant exposure is relative to nursing duration (Alstrup and Slorach, 1991). Indeed, levels of PCBs and DDE in the body decrease for a woman with previous breastfeeding, and time spent breastfeeding (Rogan

et al., 1986), so it is also necessary to consider safe ways of reducing women's exposure before it reaches the infant.

Storage in adipose tissue

Almost every report, paper, book or volume relating to endocrine disruptors describes them as lipophilic; that is they have a particular affinity for adipose tissue. On every trophic level, exposure to endocrine disrupting chemicals results in the capture of xenoestrogens and other disruptors in organic tissue. Some is excreted via hepatic and other mechanisms, but a proportion is stored in adipose tissue. As a result, EDCs are readily stored in the adipose tissue in the breast and are easily excreted during lactation, which provides a unique route of contamination for feeding infants (e.g. Dewailly, et al., 1989). Many of these compounds are especially stable with very long half-lives, so they can remain in adipose tissue for long periods, increasing in concentration as relative exposure continues.

As described, the effect of bioamplification results from exposure up the food chain initially from chemicals leached into water systems from their source, as waste material or as degraded material, which are then stored in tissues of small water life. As algae, crill and other small water and sealife are consumed by increasingly large predatory species these chemicals become stored in adipose tissue of large mammals. Predators therefore have an exposure relative to that stored in their prey and will store increasingly larger amounts of endocrine disruptors the more they eat.

More specifically, the storage of EDCs in a predator doesn't necessarily rely on the concentration of contaminants in the prey. EDCs are stored selectively and so do not necessarily match concentrations in the diet (Facemire, 2000). There is also variation in the way they are stored. Some are more lipophilic than others, and depending on whether contamination is from individual EDCs or from a mixture may alter whether the relative concentration of storage of one is

increased or inhibited by the presence of another (ibid). There is also some suggestion from studies that the type of adipose tissue would also have an effect on storage due to the number of fatty acids in the tissue (ibid). Some pesticides rapidly leave the blood and liver, and remain in adipose tissue (ibid).

Some evidence suggests that xenoestrogens are inactive while stored in adipose tissue, although there is some break down into appropriate metabolites, so over time there will be effects from stored compounds (Sharara et al., 1998; Pelletier et al., 2003). The greatest effects from stored EDCs are during periods of fat mobilisation (Facemire, 2000) when there is the possibility of xenoestrogen action on target receptors in the body, and metabolism of some compounds, which may lead to further insulting actions. Of particular importance in this scenario is weight loss (Pelletier et al., 2003). These effects are described in both the mouse model (Bigsby et al., 1997), and in humans (Jandacek and Tso, 2001).

Loss of adipose tissue stores may result in exposure of other tissues to xenobiotics, release into circulation, storage in other tissues, and reduced body burden by excretion. There is a degree of exchange between the blood and adipose tissue, brain and liver, with some of this leading to faecal excretion, other to storage, and some to mammary excretion in women (Jandacek and Tso, 2001). Some metabolism to products with different electronic charges allows toxins in adipose tissue to move within the blood, bile and urine. Faecal excretion is the main route for unchanged EDCs and their metabolites, and urine is the route for more polar compounds. This typically occurs via biliary excretion. There is evidence for non-biliary excretion, which therefore diverts EDCs from the liver (Jandacek and Tso, 2001).

This raises the concern that if mobilisation of fat stores results from a growth spurt, then girls could become vulnerable to bioavailability of stored EDCs during these periods. Around the time of the pre-adolescent growth spurt xenoestrogens could become available to target mechanisms associated with pubertal development or reproductive function. Bioavailability of EDCs during

peak height velocity (PHV) could therefore have the potential to affect age at pubertal onset and age at menarche. The degree to which this occurs would depend on concentrations of EDCs in the body, which is tied to weight status.

Organochlorines were found in higher concentrations in obese sedentary individuals compared with athletes (Pelletier et al., 2003). Although concentration per gram of adipose tissue may be less, due to a dilution effect, higher weight individuals have greater stores of adipose tissue compared with lean individuals, so the overall concentration in obese individuals is higher. They also have higher plasma concentrations of organochlorines than athletes or lean sedentary individuals, which is thought to reflect adipose tissue burden, and therefore carry a much larger burden overall (ibid). Elimination also appears quicker in lean individuals, which is likely the effect of a lower percentage of adipose tissue in which EDCs can become stored long-term (Pelletier et al., 2003). This suggests that those who are already large have greater potential for endocrine disruption during a growth spurt, not to mention that their ability to store fat may be partially influenced by obesogenic EDCs already in their systems, which may have other unknown endocrine effects, and may be absent in leaner individuals.

The consequences of mobilisation of fat mass may concentrate xenoestrogens into remaining fat tissue as they may be attracted to the remaining mass. The likelihood of mobilised EDCs reaching targets largely relies on energy balance, since it is this which determines whether or not fat stores need to be created or mobilised, which will in turn increase or decrease the concentration of EDCs in adipose tissue. Weight loss may be a risk factor in obese individuals as this will concentrate fat stores of EDCs and also expose other parts of the body to their effects. Overall energy balance will be key to considering individual levels of risk from stored EDCs.

The double burden of EDCs on Arctic populations

Inuit populations serve as the best illustrative example of pathways of EDC exposure, and the continued threat posed by chemicals with a lasting legacy.

Many of the anthropogenic compounds recognised as endocrine disruptors were designed to have long half-lives, and as a result many are incredibly persistent. This not only means they remain for long period around the areas of production, but also have the opportunity to spread to new environments. Some endocrine disruptors have been found in areas thought to be pristine, because they get incorporated into the food chain by migratory animals, air currents and water currents. The Canadian and European arctic are excellent examples of this (Giam et al., 1978; Diamanti-Kandarakis, 2009). Inuit are especially vulnerable to PCB exposure and they show levels in their blood far higher than those found in inhabitants of Southern Canada (Johansen, 2002).

Canadian arctic and polar conditions act as a cold trap for chemical pollutants. The temperatures in the arctic slow down the natural degradation and metabolism of these compounds so that they persist and remain stable much longer than if they were at lower latitudes. So chemicals and pesticides that were used 30-40 years ago, but have since been banned or limited in other areas, are found in surprisingly high concentrations in and around the arctic and as a common element of the arctic biota. They become lodged in the food chain through marine and land mammals, and consequently end up at the highest trophic levels: humans. Inuit are particularly at risk from a traditional diet of "country food", which consists of sea fish and mammals, including much of their blubber where these chemical pollutants are stored. This is outside of their historical experience and they see themselves as the "miners' canary" of the arctic (Johansen, 2002). This exposes numerous arctic populations of Inuit to a double burden: high levels of EDCs carried to their region and incorporated into their natural food sources, and the burden of the continued stability of these compounds in their native regions.

Not only are Inuit, like the Sami in Europe and the Cree in Canada, exposed to these disruptive compounds in high doses, but they are at an increased risk of a high POP burden because they have a relatively high weight for height, as seen in Inuit children when compared with children in the USA (Jamison, 1990). There is also evidence from a study in Greenland that overweight is increasing among children in Polar Regions (Niclasen et al., 2006), which could lead to earlier age at puberty. Indeed one study gives some indication as to menarcheal age among Inuit people. In a study of 290 girls in Greenland the mean age was 12.64 years, which is comparable to European and North American populations (Becker-Christensen, 2003). Classically maturation among the Inuit was thought to be much older (see Bojlen and Bentzen, 1968 for an overview), which could be due to previous error, or the risk of greater stores of endocrine disruptors in children with higher fat levels, contributing to earlier age at maturation.

Knowledge of endocrine disruptors within arctic communities is mixed. Some feel that if they live further away from the ocean they don't have the same risks as those coastal populations, and stigmatise those they believe do, as diseased. But many women are scared to breastfeed wherever they live because they have been told that they can pass chemical pollutants through their breast milk to their feeding infant. Indeed, there is evidence of high levels of PCBs in the breast milk of Inuit women compared with controls (Dewailly et al., 1989), which places children breastfeeding from these mothers at risk of contamination via a mechanism usually considered to be beneficial and protective (ibid). Another widely held belief is that stories about chemicals causing illness in their children is another scare tactic targeted at them to reduce whaling and hunting (Colborn et al., 1996). As such, one author has highlighted the need to understand how immediate Arctic populations judge the threat of EDCs to be (Bjerregaard, 1995).

Despite this there is work in place to protect Arctic peoples. The Stockholm treaty was put in place to restrict and ultimately eliminate the production, use, release and storage of persistent organic pollutants. (UNEP, 2010).

Low-dose response and nonmonotonicity

While we have a lot of convincing evidence for the effects of EDCs at low levels it is not difficult to understand why the low dose effects of anthropogenic compounds were ignored, or simply not considered, when one considers classic toxicological thinking. Typical toxicological screening works on the assumption that response is relative to dose, and so cells are exposed to increasingly higher doses of a toxin in order to understand their response. It was simply not in the interests of toxicologists to understand the impact on corporal mechanisms from environmental chemicals at naturally meaningful levels; only to determine which doses result in death (Heindel and vom Saal, 2009; Patisaul and Adewale, 2009). When low dose effects were considered, high-dose single substance experiments were extrapolated to low levels, which is an inexact and flawed method that did not accurately measure relative effect.

EDCs may have different actions at low doses compared with larger exposure, which is the case with some endogenous hormones (Vandenberg et al., 2012). This could be due to special properties that create effects at low doses that disappear at high doses, or some kind of feedback mechanism. This is a non-monotonic effect, and is seen with DDT, which is a potent neurotoxin at high levels, but interacts with androgens and oestrogens at low doses and therefore does not follow the classic linear monotonic effect of toxicity (Patisaul and Adewale, 2009) (see figure 3.2). Xenoestrogens may also be active at levels much lower than those usually tested in toxicology screens (EDEN, 2007), which highlights the importance of understanding their actions in all scenarios when effects at high dose cannot predict effects at low dose (Vandenberg et al., 2012).

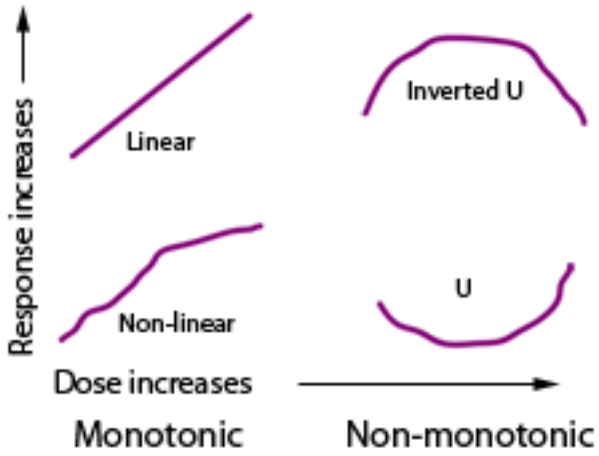

Figure 3.2 Example of non-monotonicity from Myers and Hessler, 2007.

This raises the issues of testing for unique mixture effects of xenoestrogens (Diamanti-Kandarakis, 2009; Muncke, 2009), as well as seeking information on exposure during sensitive life stages, which are since shown to be a risk period for the influence of EDCs on the development of various processes (Muncke, 2009).

Phytoestrogens and endocrine disruption

The interest of some western populations in the so-called healthful behaviour of a soy-based diet may be cause for concern. This particular dietary choice is believed to reduce the risk of cardiovascular diseases, and reduce rates of cancers associated with reproductive hormones since soya products contain phytoestrogens, which may be protective against these conditions. Many foods and drinks naturally contain phytoestrogens, lignans and isoflavonoids (Patisaul and Adewale, 2009). However, with supplements and a soy-based diet, including infant formulas, people are ingesting levels well above what may be naturally tolerable, and above the traditional East Asian soy diets (ibid). Could this be a cause for concern regarding endocrine disruption? Can we be sure about the ways in which elevated levels of phytoestrogens interact with endogenous oestrogens? There are limited human-based studies that describe the effect of phytoestrogens on sexual development, but results indicate that premature

thelarche is more common in infants fed on soy-based formula compared with peers (Freni-Titulaer et al., 1986; Zung et al., 2008).

Phytoestrogens may act in the same way as some other seemingly harmless plants like clover to deter animals from eating from them. Clover was shown to be a potent natural fertility inhibitor (Colborn et al., 1996). The natural defences of the plant interfered with animal steroid hormone levels to such a degree that animal organisms were unable to reproduce. Therefore, the same effect could be seen in adults exposed to phytoestrogens, and even more worrying, could upset the natural reproductive development of children exposed to exogenous oestrogens via a diet seen to be beneficial to health. Further, soy-based genistein in infant formula is positively associated with adult obesity (Newbold et al., 2009). This could be confounded by the high energy-density of formula (ibid), but it could also signal a greater picture of endocrine disruption from seemingly healthful compounds, since circulating levels of phytoestrogens are thousands of times higher than endogenous oestrogen levels in formula-fed infants fed on soy (Cederroth et al., 2012).

There is inconclusive evidence surrounding the risks of phytoestrogens, i.e. isoflavins on growth and development, or indeed endocrine disruption. This could be lack of evidence or the lack of understanding of the ways isoflavins work with other EDCs and how their actions may be confounded by other endocrine insults (Cederroth et al., 2012).

Xenoestrogens and pubertal development: a mismatch between strategy and environment

Xenoestrogens present what is sometimes referred to as a mismatch between Stone Age genes and space age environments. There is a selective advantage to younger age at maturation in risky and uncertain environments (e.g. Ellis and Garber, 2000) but teen pregnancies are generally viewed as maladaptive and risky in much of the clinical literature particularly in girls less than 15 years old (e.g. Super, 1986; Klein, 2005). While we may theoretically be able to produce more young more quickly through early maturation(Biro et al., 2009) EDCs

present a double-edged sword whereby their possible role in the further acceleration of age at pubertal development increases women's risks of reproductive cancers due to greater exposure to xenoestrogens that could promote oestrogen-related cancers or exacerbate the risks associated with endogenous oestrogens.

The focus of the effects of EDCs on pubertal development stems from knowledge of the interaction with reproductive cancers but also due to the trends in pubertal development, which coincide so closely with the development of synthetic compounds that have found their way into industry and domestic life all over the globe. EDCs effects on reproduction are not limited to pubertal development. The term "ovarian dysgenesis syndrome" covers the different reproductive system responses to EDCs (Buck and Louis et al., 2011). It encompasses syndromes that have an environmental element to their aetiology. This includes developmental abnormalities in the uterus, urinary tract and vagina, as well as hormone-related disorders such as polycystic ovary syndrome (Fowler et al., 2012).

It is hard to know at what point different organs and tissues are affected, and it is very difficult to assess retrospective actions of EDCs on fetal and early developmental processes, but there is a lot of evidence to suggest that EDCs act directly on the gonads (Bourguignon et al., 2010). With more evidence also suggesting that EDCs may play a large role in the obesity epidemic, there is a story emerging of interactions between the two processes. Experimental work suggests that exogenous chemicals interfering with targets relating to growth, lipid metabolism, and differentiation and functioning of brain, gonads, and adrenals may play a role in the link between birth outcome, growth and puberty development (Schoeters et al., 2007).

We do know more about the actions of individual chemicals on female pubertal development. For example phthalates act as anti-androgens, which would affect the oestrogen-androgen ratio and initiate breast development. Phthalates could

therefore be active in early breast development (McLachlan et al., 2006). One study looked at the extremely high levels of premature thelarche in Puerto Rico and found that girls had very high serum levels of phthalates (Colon et al., 2000). Puerto Rico has the highest incidence of premature thelarche in the world, which has been attributed to high phthalate exposure from the agricultural industry (Ibid).

A study of Chinese women working in a textile factory found that menarche occurred earlier, and there was a higher chance of short menstrual cycle length in response to DDT exposure (Ouyang et al,. 2005). DDT and PCB exposure may also lead to reduced fecundability in European Inuit women. The lowest age at menarche was found in Greenlanders in the study, but there was little effect in terms of cyclicity. So, exposure to certain EDCs may lead to earlier age at maturation, but effects of cycle regularity and length may be controlled by genetic or nutritional factors (Toft et al., 2008).

Some endocrine disruptors may be a cause of intra-uterine growth retardation (IUGR), which results in changes to pubertal development in the affected individual in later life as a consequence of extensive catch-up growth (Schoeters et al., 2007). However, this interpretation of altered development does not account for endocrine-disrupting mechanisms other than those affecting intra-uterine growth, which could be altering the timing and tempo of puberty.

In an animal model, it was shown that BPA accelerated age at puberty in the female mouse. However, the rate at which this occurs may be relative to levels of endogenous oestrogens, which could alter sensitivity to chemical oestrogens (Howdshell et al., 1999). BPA is also found in high levels in women suffering from PCOS Tsutsumi, 2005). This could be the result of androgen-related metabolism of BPA, since it is also higher in normal men. BPA may be either stimulating testosterone production, or testosterone could block BPA metabolism (ibid).

Estrogens are already present at negligible levels in young children well before pubertal development is triggered by release of the pulsatile GnRH signal. Given that endocrine disruptors act in parts per trillion, it is hardly surprising that they have the capacity to cause disruption to reproductive development by interfering with these sensitive steroid levels, and indeed defy the classic rules of toxicology. While the evidence for the role of EDCs in the recent acceleration of female pubertal development is not exhaustive, the suggestion of an adverse role on reproductive function might account for a degree of variation that cannot be explained by diet or genetic influence on maturation.

Endocrine disrupting chemicals and the obesity epidemic

As discussed above, there is an important relationship between EDCs and energy balance. In addition to the role adipose tissue plays in storing endocrine disruptors, some oestrogenic chemicals are found to increase the incidence of obesity. Indeed, the rise in obesity prevalence matches that of the use of industrial chemicals (Colborn et al., 1996). Different synthetic oestrogen mimics result in a number of mechanisms that can increase adipogenesis. Any chemical or disruptor that inappropriately regulates adipogenesis and promotes obesity is known as an obesogen (Grun and Blumberg, 2007; 2009).

Obesogens impact obesity via changes in gene expression, which are caused by epigenetic changes. More specifically endocrine disruptors affect a receptor called PPAR gamma, which in one state will allow cells to remain as fibroblasts (a type of stem cell), and in the other will push them towards becoming fat cells via the production of more preadipocytes (Grün and Blumberg, 2007). In children who are increasingly sedentary and over-nourished this could increase their ability to store fat, which children are consuming in higher levels.

EDCs could also be altering metabolic actions and tempo, creating a new weight set point as a result of exposure during critical periods of development (Grün

and Blumberg, 2007, 2009; Heindel and vom Saal, 2009; Newbold et al., 2009). If metabolic mechanisms are set to hoard calories, this may explain why some individuals simply cannot lose weight when they eat the same amounts and exercise just as much as their slimmer counterparts. If EDCs are affecting a minority of the overweight or obese population, their condition could be out of their control highlighting an unrecognised public health risk. (Begley, newsweek). This is not to say that all overweight individuals can put their weight issues down to pre-programming or chemical contamination; some individuals simply eat too much and exercise too little.

BPA has specifically been shown to act as an obesogen. BPA can reduce insulin sensitivity leading to insulin resistance. Doses of EDCs can upset pancreatic physiology, leading to changes in regulation of glucose and lipid metabolism (Diamanti-Kandarakis, 2009). More directly BPA can do this by suppressing adiponectin, which is an insulin sensitizer and stimulates IL-6 and TNFα, which increase the chance of insulin resistance. BPA therefore contributes to the development of the metabolic syndrome (Ben-Jonathan et al., 2009, Hugo et al., 2008). These mechanisms are associated with energy metabolism pathways; other endocrine disruptors have also been shown to upset these pathways, particularly mitochondrial respiratory chain (MRC) oxidative phosphorylation and adenosine nucleotide translocator ANT shuttles, both associated with glucose transport (Chen et al., 2009).

In the same way that endocrine disruptors have been shown to behave differently as mixtures of compounds compared with single-chemical doses, those that act as obesogens should be considered in the same manner. We can understand this with regard to PCBs. Specific mixtures, potency, or concentration of chlorine in PCBs may alter the chemical structure such that we can explain the different effects of higher and lower chlorinated PCBs on the onset of puberty. Their structure may alter binding affinities, making their actions unique to concentration of chlorinated biphenyls (Dickerson and Gore, 2007).

Further research into the effects of xenoestrogens and other EDCs on female pubertal development and the relationship of those effects with obesogens will highlight specific risks for girls. This research will also direct clinicians and other healthcare professionals in the treatment and advice for girls who have been exposed to EDCs, or advise them on ways to decrease their risks of exposure.

EDCs in relation to pubertal trends in the UK

The potential for interaction between EDCs, weight status and pubertal maturation is overwhelming. As individuals in the UK get heavier, particularly children, then they are at higher risk of greater overall burden of lipophilic environmental pollutants than leaner peers. Everyday exposures may be contributing to earlier female maturation by: 1) interacting with the neuroendocrine mechanisms that control pubertal development, specifically disrupting or blocking the actions of oestrogens and androgens; and 2) accumulating in the adipose tissue of pre-adolescent girls and accelerating puberty, specifically age at thelarche.

Heavier girls may already have a tendency towards earlier maturation (as detailed in Chapter one), but as their growth accelerates at the beginning of puberty (Bogin, 1988) they are potentially encouraging the bioavailability of a cocktail of EDCs, which could further accelerate the process. EDCs may therefore account for a significant proportion of the variance in age at menarche and age at pubertal onset in the UK and elsewhere that weight status alone cannot.

In Part I, I have discussed physiological and environmental influences that determine the timing and process of female pubertal development in a variety of ecological settings. This discussion provided a background to understanding and measuring the physiological changes associated with female puberty, as well as discussing evidence for a secular trend for accelerated female pubertal development in a number of western populations. Moreover, I outlined the variety in the female pubertal process that deviates from the western model of

normal tempo and progression through puberty, and discussed the limitation of this biomedical model to describe phenotypic plasticity in the process of puberty in a way that recognises a range of normal, rather than healthy versus pathological maturation. Finally, I outlined the novel influence of endocrine disrupting chemicals on the timing and tempo of female puberty and their potential role in the acceleration of pubertal onset. All of the physiological and environmental influences on female pubertal development discussed in Part I provide the context and possible drivers for a continued secular trend in female pubertal development in the UK, and also provide a framework for considering how the tempo and process of female pubertal development in the UK can be considered as an adaptive response to the environment.

In Part II, I will analyse the influence of overweight and obesity on female pubertal development, as well as analyse longitudinal data from the UK to investigate evidence for acceleration in female pubertal onset over the last 60 years and the factors responsible for that change.

Part II

Chapter Four: The effects of overweight and obesity on female pubertal maturation: a systematic review

Abstract

Background: Recent literature based on analyses of longitudinal data sets in the USA and Europe finds a continued secular trend in girls for younger age at menarche. Other authors argue that menarche has remained stable and it is the age at *onset of puberty* that has reduced in recent decades. There is also a concurrent trend towards higher rates of overweight and obesity among young girls as a result of increased sedentism and a diet high in fat and sugar. A number of recent publications propose that the decline in age at puberty and increasing weight of young girls are causally related such that the latter directly accelerates age at menarche. I therefore undertook a systematic review of literature to find evidence for this phenomenon.

Objectives: Given the controversies surrounding age at maturation in females this review will: 1) collate current understanding of the effect(s) of overweight and obesity on female pubertal maturation; 2) understand how resulting changes in pubertal development may or may not deviate from a traditional Tanner model of maturation; 3) look for a continued secular trend in age at menarche; and 4) look for evidence of an earlier age at pubertal onset.

Methodology: 57 articles were reviewed following two systematic literature searches. Keywords and MeSH search terms: body weights and measures (MeSH), adipose, adiposity, BMI (MeSH), body size (MeSH), body weight (MeSH), Obesity (MeSH), Overweight (MeSH), sexual development (MeSH), Sexual maturation, pubic hair, breast development, puberty (MeSH), menarche (MeSH), Adrenarche (MeSH), thelarche, gonadarche, child, infant, teen, adolescent. Databases: Medline/PubMed, Embase and the International Bibliography of the social sciences (IBSS). The search produced 6935 results, which were first de-duplicated, then reviewed for relevance by title and abstract and finally by full text.

Results: Although there is evidence in the USA for a continued secular trend in both age at menarche and pubertal onset there is insufficient evidence to determine the same effect globally. There is, however, a strong degree of consensus that girls who are overweight or obese begin puberty earlier than normal weight peers. Additionally, there is evidence for asynchronous pubertal development, particularly among overweight and non-white girls, whereby girls begin breast development significantly earlier than the onset of pubic hair growth. Much needs to be done to understand the specific mechanisms behind these phenomena.

Introduction

Rationale

There is overwhelming evidence for a link between increased weight status and earlier female pubertal onset. This association is explained within the framework of LHT since increased weight status suggests positive energy balance that could tip the body's division of resources in favour of earlier maturation. However, while we have evidence of a strong link, there is little evidence of the mechanisms involved. An early suggestion from Frisch and Revelle (1970; 1971) claimed that a minimal weight of 48kg signals that the female body is capable of beginning reproductive function. This threshold theory has been largely discredited, since there is both little evidence for a threshold mechanism, and other measures of height and skeletal development better predict age at menarche (e.g. Ellison, 1982).

While there may not be a critical fat mass that triggers a response in the HPO so that heavier girls mature at younger ages, it has been proposed that positive energy balance associated with overweight likely contributes to mechanisms associated with pubertal maturation (e.g. earlier height gain) (Rogol et al., 2002; Ebling, 2005). Furthermore, age at maturation may be relative to the length of time spent in positive energy balance since energy allocation towards maturation could occur sooner. In fact, both Rogol et al. and Ebling (2005) highlight the importance of energetic reserves and energy intake relative to size,

as indicators of the body's capacity to maintain reproductive function, and suggest that long-term measurement of energy intake versus expenditure could signal when pubertal onset would maximise reproductive potential (Rogol et al., 2002; Ebling, 2005).

A number of studies directly link earlier obesity and earlier increases in weight relative to normal weight peers with an earlier pubertal onset (e.g. Lee, 2007; Terry et al., 2009; Morris et al., 2010; also see Dunger et al., 2006). Accelerated age at pubertal onset may be indicative of earlier, and perhaps a longer period spent in positive energy balance. It is also possible that associations between weight at given stages in childhood and early maturation may be indicative of critical growth periods where there are mechanisms by which the body is able to evaluate the environment and adjust trajectories accordingly (Barker et al., 1989; Hales and Barker, 1992; Barker, 1997). Furthermore, excessive eating at a given time in early childhood may interfere with these growth windows and alter the course of maturation. For example, the early adiposity rebound (AR) -the point where a child's body fatness declines to its lowest level and then increases, typically around age 5-6 years (Whitaker et al., 1998)- has been linked with adolescent obesity, which we know is a greater risk for early pubertal onset (see Whitaker et al., 1998).

But what is driving this response? Earlier weight gain and an extended period of positive energy balance may contribute to an earlier pubertal onset as the result of the monitoring effect of the hormone leptin. Leptin is a neuroendocrine hormone produced in white adipose tissue that forms part of the mechanism for appetite regulation and satiety, as well as control of energetic reserves. It is synthesised in proportion to energy reserves and signals those reserves to the hypothalamus via a feedback mechanism (Zhang et al., 1994). There are also leptin receptors in the hypothalamus that synthesize GnRH, and it has been found that those individuals deficient in leptin fail to initiate puberty (Ong et al., 1999). However, although a deficiency in leptin affects normal pubertal development, there is no definitive evidence that a threshold level of leptin

initiates pubertal development. The monitoring effect of leptin may therefore be permissive whereby leptin behaves as a 'metabolic gate" that allows puberty to proceed if energetic conditions are suitable (Cheung et al., 1997). In the presence of overweight or obesity, those conditions may be achieved at an earlier age.

More recently neurokinin B - a peptide and member of the substance P-related tachykinin family - is suggested as a possible pubertal trigger since it is highly expressed in hypothalamic neurons (Topaloglu et al., 2009). Understanding how neurokinin B interacts with weight status is important for advancing knowledge of the mechanisms that could lead to earlier pubertal onset in overweight and obese girls.

Given the particular risk for early age at pubertal onset for girls born small for gestational age (SGA) who also experience weight gain in the form of catch-up growth during childhood (Ibanez and Zegher, 2006; Ibanez et al., 2006)(Discussed in chapter one), coupled with evidence for earlier pubertal onset as the result of overweight and obesity, it is also important to consider the variation in pubertal onset that might result from increased weight in childhood.

Although girls born SGA seem to show development of pubic hair (pubarche) before breast development (thelarche), there is an emerging trend for earlier breast development among obese and overweight girls born appropriate for gestational age (AGA) (Herman-Giddens et al., 1997; Schubert et al., 2005). The classic Tanner model is a process whereby breast development begins on average just before the eleventh birthday, with pubic hair growth following soon after (Tanner, 1989, chapter 5). In contrast, Herman-Giddens et al. (1997) and Schubert et al. (2005) note asynchronous development with breasts developing well before the eleventh birthday in some cases, and certainly a significant period before pubarche. Herman-Giddens et al. (1997) and Schubert et al. (2005) analyse cross-sectional data from 2104 girls attending specialist clinics and around 17,000 girls in the NHANES III data set respectively. Although this both eliminates the benefits of longitudinal study as employed by Tanner and

colleagues, and introduces bias when reporting only on girls who have begun development early, it does highlight concern among clinicians that they are seeing *more* girls developing earlier than the typical Tanner model.

Dunger et al. (2005) also suggest a growing trend for earlier age at breast development in a review of various longitudinal and cross-sectional studies relating to the effect of obesity on growth and puberty. They suggest that menarche may not be advancing at the same rate as breast development, if at all. Conversely, an expert panel (Euling et al., 2008) agreed that data is sufficient to deem that there is an earlier onset of breast development as well as menarche, although unlike Dunger et al. (2005) whose data is from a variety of regions, Euling et al. focus on changes based on longitudinal data from the USA only. As Euling et al. (2008) suggest there is still uncertainty as to whether overweight is simply encouraging earlier development of particular pubertal markers, or whether it is accelerating the entire process, but uncertainty also remains over the degree to which age at menarche is accelerating outside of the USA, and whether this is the result of overweight and obesity. As such there is a sustained interest in the effects of weight status on maturation, particularly in light of recent increases in both childhood overweight and obesity, coupled with sedentary behaviours.

objectives

This systematic review will 1) collate current understanding of the effect(s) of overweight and obesity on female pubertal maturation; 2) understand how resulting changes in pubertal development may or may not deviate from a traditional Tanner model of maturation; 3) look for a continued secular trend in age at menarche; and 4) look for evidence of an earlier age at pubertal onset.

Methodology

A systematic review relies on predetermined search criteria formulated from search terms appropriate to the area of research. This method is described in

Khan et al. (2003). This particular methodology is not only rigorous, but the systematic nature of data collection makes is possible to collate information in both a clear and consistent manner.

The systematic review was undertaken using topic-specific search terms. The search terms used were searched as both MeSH (medical search headings) terms where possible and as keywords. This method was employed to capture any studies that were relevant but may not have been included under MeSH, as these terms are assigned manually. The initial literature search was undertaken in December 2009 and a second round was undertakes in December 2010 to capture relevant studies from the intervening 12 months.

Eligibility and rationale

This systematic review was carried out in order to inform a larger analysis of pubertal trends in the UK, which will be detailed in the following Chapter of this thesis. The datasets analysed within Chapter five are as recent as 2010, which set a period of time by which to limit the literature search in this chapter. Searches were also limited to human studies, in order to determine what is known specifically about the interaction of weight status and pubertal development in girls rather than models from animal studies broadened to humans in a theoretical capacity. Finally, studies were chosen that focused on pubertal development before age 18 in order to rule out studies that focused on pathologically late pubertal development.

Information sources

Publications were searched in Medline/PubMed, Embase and the International Bibliography of the social sciences (IBSS).

Search

Table 4.1 (overleaf) contains a reproducible search method used in all of the databases for this review. The search uses MeSH terms and keywords combine with Boolean logic.

Study selection

Table 4.2 (page 97) outlines the exclusion criteria after the initial literature search. Primary exclusion criteria determine date and study subjects, and secondary exclusion criteria determine study type.

Data items and collection process

Data extraction variables are listed in table 4.2. I independently extracted this data from each paper where it was available.

Table 4.1. Database search method.

Search Criteria

Weight Status	**Pubertal Development**	**Age**
Body weights and measures (MeSH)	Sexual development (MeSH)	Child
Adipose	Sexual maturation	Infant
Adiposity	Pubic hair	Teen
BMI (MeSH)	Breast development	Adolescent
Body size (MeSH)	Puberty (MeSH)	
Body weight (MeSH)	Menarche (MeSH)	
Obesity (MeSH)	Adrenarche (MeSH)	
Overweight (MeSH)	Thelarche, Gonadarche	
Combined with Boolean OR command	**Combined with Boolean OR command**	**Combined with Boolean OR command**

Combined with Boolean AND command

Bias

Risk of bias was determined at the study level. Studies were checked for any funding criteria or sponsorship that would compromise the integrity of the reported results, or explain heterogeneity of results.

Synthesis of results

No meta-analyses were carried out on these data. This systematic review contains a small number of studies with numerous study designs and outcome measures, which provides very little data for comparison. These data do not lend themselves to a rigorous statistical analysis. Instead, the data are presented as a discussion of the various factors that form the relationship between overweight and obesity, and female pubertal development.

Table 4.2. Systematic literature search and exclusion criteria.

Search Terms	Primary Exclusion Criteria	Secondary Exclusion Criteria	Data Extraction Variables
Weight Status	Published prior to 1/1/2010	Case studies	Author
Body weights and measures (MeSH)			
Adipose	Non-human	Clinical studies of biomedically defined precocious puberty	Year
Adiposity			
BMI (MeSH)	Male		Area of collection
Body size (MeSH)		Endocrine abnormalities	
Body weight (MeSH)	Gestation studies		Time frame
Obesity (MeSH)		Other chronic illness	
Oberweight (MeSH)	Focus on post-18 years of age		Number of Participants
		Conference abstracts	
Pubertal Development			Age of participants
Sexual development (MeSH)			
Sexual maturation			Study name
Pubic hair			
Breast development			Study design
Puberty(MeSH)			
Menarche (MeSH)			Ethnicity
Adrenarche (MeSH)			
Thelarche			Outcome measures
Gonadarche			
			Main findings
Age			
Child			Control measures
Infant			
Teen			Average age at menarche
Adolescent			

Results

Figure 4.1 summarises the literature search results and selection process.

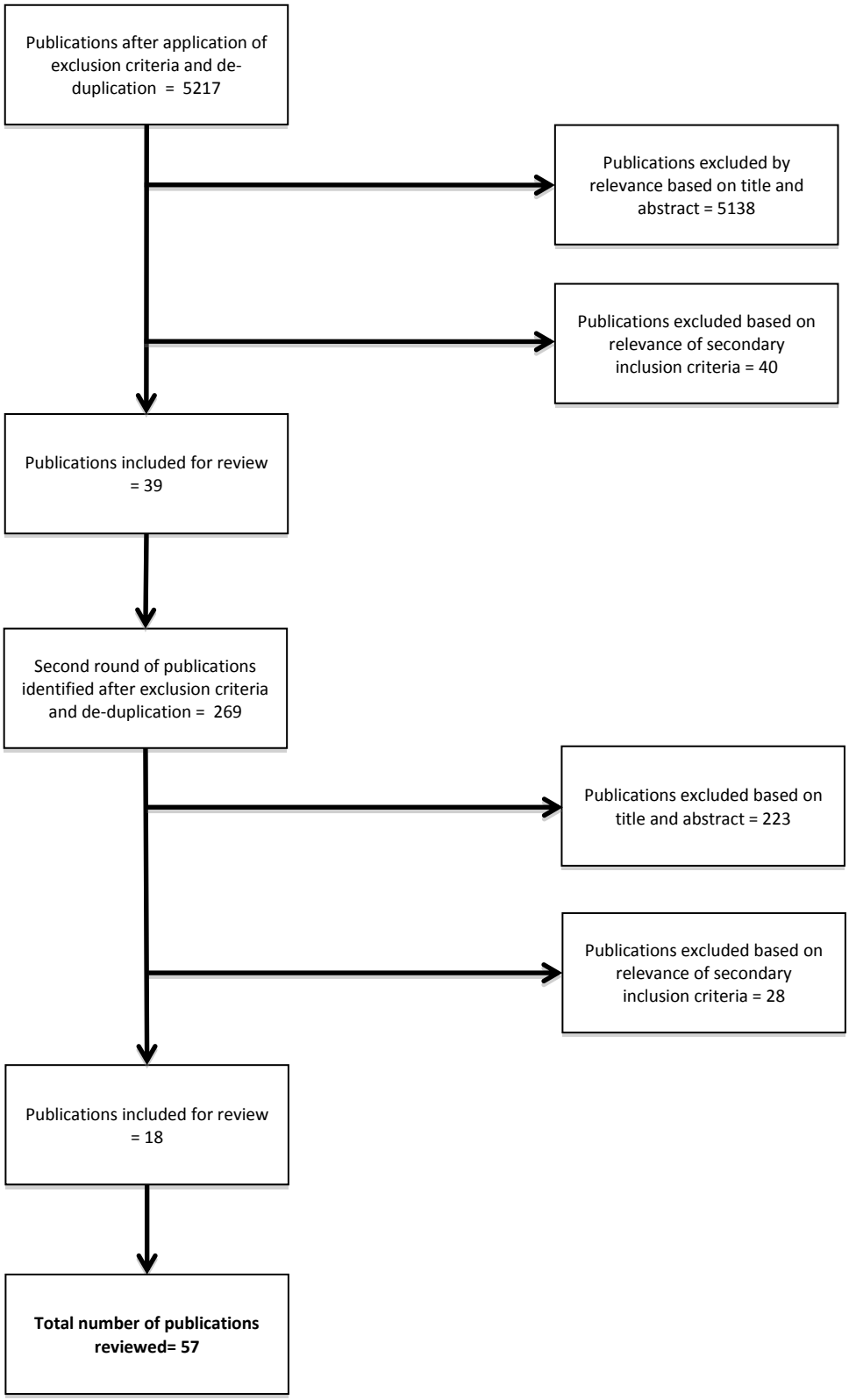

Figure 4.1. Summary study selection flow chart

What emerged from the literature search and subsequent readings are a number of themes that can be associated with the impact of overweight and obesity on pubertal maturation. These themes included: BMI/overweight and maturation, skeletal maturation, synchronicity of maturation (that is the process of simultaneous breast and pubic hair growth), body composition (body shape and fat patterning), metabolism, socioeconomic status (SES), ethnicity, and catch-up growth.

There was a significant spread of age and cohort size across these studies ranging from group sizes of 96 (Lin-Su et al., 2002) to 10,759 children (Kaplowitz et al., 2001), and an age ranging from birth to eighteen years. The oldest data come from two longitudinal UK studies: The Medical Research Council National Survey of Health and Development (NSHD) beginning in 1946, and the Newcastle Thousand Families Study beginning in 1947 (Blell et al., 2008), both of which are still collecting data.

Table 4.3. Reported age at menarche.

Author(s)	Place	Years	Average age at Menarche (yrs)
	N. America		
Demerath et al (2004)	USA	1929-46, 1947-64, 1965-83	12.7 12.8 12.6
Berkey et al (2000)	USA	1930-1949	12.83
Terry et al (2009)	USA	1959-1963	White: 12.53 African American: 12.70 Puerto Rican: 12.14
Anderson, et al. (2003)	USA	1963-1970, 1988-1994	12.75 12.54
Freedman et al (2003)	USA	1973-74, 1992-94, 1982-96.	12.9 for white girls 12.8 for black girls
Biro et al (2003)	USA	1986/87-1996/97	12.6
Anderson and Must (2005)	USA	1988-1994, 1999-2002	12.53 12.34
Lin-Su et al (2000)	USA	1999-2000	Obese 11.87 overweight 12.14, normal weight 12.20
	S. America		
Martinez et al. (2010)	Brazil	1982	12.44
Torres Mejia et al (2005)	Mexico	1998-99	12.0
	Europe		
Morris et al (2010)	UK		12.7
dos Santos Silva et al (2002)	England	1946-2002	13.1
Blell et al (2008)	England	1947-1997	12.94
Okasha et al (2001)	Scotland	1948-1968	Dropped from 13.2 to 12.5
Rubin et al (2009)	England	1991-present	Median: 12.93
Christensen et al (2010b)	England	1991-present	12.9
Heger et al (2008)	Sweden, Germany	1950-1980.	lean 14.3, normal 13.3, obese 12.9.

Bau et al (2009)	Germany	2006-2007	12.8 average. Obese/overweight- 12.5, normal- 12.9, underweight- 13.7
Koziel and Jankowska (2002)	Poland	1996-1997	12.7
Mandel et al (2004)	Israel	1980	Obese 12.9, normal 13.3, lean 13.5
Rigon et al (2010)	Italy		12.40
Papadimitriou et al (2008)	Greece	2008	Obese- 11.73, normal- 12.29, lean- 12.42
Semiz et al (2009)	Turkey		12.41
	Africa		
Torres Mejia et al (2005)	Egypt	1997	13.0
Goon et al (2010)	Nigeria		Mean: 13.02
			Median: 13.00

Overweight and maturation

Thirty-four studies focus on the effect of childhood weight status on maturation and found a negative correlation between weight or body mass index (BMI) and sexual maturation in girls, whether by menarcheal status or Tanner stage (Anderson et al., 2003; Anderson and Must 2005; Bau et al., 2009; Biro et al., 2003; Blell et al., 2008; Christensen et al., 2010b; Davison et al., 2003; dos Santos Silva et al., 2002; Freedman et al., 2003; Frontini et al., 2003; He and Karlberg 2001; Heger et al., 2008; Himes et al., 2004; Kaplowitz et al., 2001; Koziel and Jankowska 2002; Lassek and Gaulin 2007; Lee et al., 2007; Lin-Su et al., 2002; Mamun et al., 2009; Moayeri et al., 2006; Martinez et al., 2010; Morris et al., 2010); Okasha et al., 2001; Papadimitriou et al., 2008; Ribeiro et al., 2006; Rigon et al., 2010; Rubin et al., 2009; Semiz et al., 2009; Sloboda et al., 2007; Tam et al., 2006; Terry et al., 2009; Torres-Mejia et al., 2005; Wang 2002; Williams and Goulding, 2009). Of these studies thirteen were based in the USA, four in the UK, two in Germany and central Europe, two in Australia, one each in Greece, Sweden, Poland and Iran, and one comparing Mexico and Egypt. Five of the studies from the USA used data from the NHANES (National Health and Nutrition Examination Survey) II or III study (all five included NHANES III data), and two examined data from the Bogalusa heart study. Two UK studies examined the Avon Longitudinal Study of Parents and Children (ALSPAC).

A number of these studies found that higher weights at different stages of infancy and childhood were predictive of an earlier onset of puberty or more advanced stage of maturation during puberty at a given age relative to peers. These include: high birth weight (Blell et al., 2008), high weight in early childhood (Martinez et al., 2010), high BMI-Z score at age 3 (Lee et al., 2007), a higher BMI at age 5 (Mamun et al., 2009), one standard deviation away from the normal weight at age at 5-6 years (Freedman et al., 2003), a higher weight at age 7 (Terry et al., 2009; Morris et al., 2010), higher weight age 8 (Tam et al., 2006; Sloboda et al., 2007), higher height weight and BMI age 8 (Rubin et al., 2009) higher weight age 9 (Blell et al., 2008) and high BMI recorded close to age at menarche (Rigon et al., 2010). Additionally, two studies found that early age at adiposity rebound (AR) is linked with an earlier age at menarche (Lee et al., 2007; Williams and Goulding, 2008). Lee et al (2007) note specifically that a high rate of change between the ages of 3 and 6 is a predictor of early maturation. Salsberry et al., (2009) divided girls by ethnicity and found that earlier maturation was associated with higher BMI by age 3 in African American girls, and by age 6 in white girls.

In contrast, some studies did not find a link between overweight and early maturation. Kaplowitz et al. (2001), for example, found that late maturers were just as likely to be overweight as early maturers. Another study of girls in Berlin found a negative correlation between BMI and age at onset of menarche, but did not see an acceleration in the age of menarche as would be expected in a population with a higher than 10% rate of obesity (Bau et al., 2009).

In the Fels longitudinal study, Demerath et al (2004) found a significant increase in average BMI between the 1947-1964 and the 1965-1983 cohorts, although overweight as measured from BMI was not significantly greater in early-maturing girls than later developers until after menarche in any cohort. The rate of increase in BMI was not accompanied in this study by a decrease in age at menarche. This indicates that early age at maturation and increasing weight may be independent phenomena (Demerath et al., 2004).

These results show *some* evidence that overweight may influence *acceleration* of age at maturation. But since this is not the case in all the papers in this review there are likely other factors interacting with weight and/or maturation. So although obesity may affect maturation, it may be through indirect mechanisms that are more subtle and sensitive. The papers that found associations with weight at given stages in childhood may be indicative of critical growth periods where there are mechanisms by which the body is able to evaluate the environment and adjust trajectories accordingly (Barker et al., 1989; Hales and Barker, 1992; Barker, 1997). In particular changes in body weight between ages 5 and 9 could be associated with, or affect adrenarche and hormones associated with this stage of development, which would in turn have an effect on the onset of puberty and age at menarche (Dhom, 1973 in Campbell, 2006; Campbell, 2006).

In contrast to the results of Demerath et al., an earlier study of the Fels longitudinal data, which focused only on the initial cohort of individuals born between 1929 and 1946, found early-maturing girls were heavier and taller than late-maturing girls. They were heavier not only during and directly following puberty, but from the age of 7 1/2 (Reynolds, 1946). While both used menarche as a measure of maturation Reynolds findings were based on weight in kilograms, whereas Demerath et al., used BMI as a measure of relative weight, which might explain the discrepancy, and may also explain the degree of variation in results.

The secular trend

Between the 1930s and the new millennium, average age at menarche in the United States appears to have declined from 12.8 to 12.3 years (see table 4.3). Two large cohort studies from the USA demonstrate this trend. There was a small, and non-significant drop in the FELS longitudinal study of 1929-1983 (Demerath and Li, 2004), but the NHANES III data showed a 2.5-month drop in age at menarche between 1963 and 1994 (Anderson et al., 2003), and a similar decrease by 2.3 months in the following ten years (Anderson and Must, 2005). Considering the changes from the 1960s onwards in the NHANES data it is likely

that most of the change in the FELS data is accounted for during the latter years, and is largely influenced by a changing diet and lifestyle among children. This is corroborated further by evidence that menarcheal age is slightly more robust between 1929 and into the 1960s. This trend is in accordance with the secular trend described by Tanner whereby age at menarche reduced some 4 months per decade from 1830 in response to favourable conditions (Tanner, 1962).

Variation in age at menarche

There is no strong evidence of a secular trend outside of the USA in these studies. However, there is evidence of a large degree of variation in age at menarche.

Two large cohort studies from the UK describe average menarcheal ages that are slightly above the US averages. Blell et al. (2008) found an average menarcheal age of 12.94 years in The Newcastle Thousand Families Study (1947-present). Girls were followed from birth, and menarche occurred over the late 1950s into the early 1960s among the cohort. Dos Santos Silva et al. (2002) found that girls who were followed over the same period in The Medical Research Council National Survey of Health and Development (NSHD) (1946-present) reached menarche at an average of 13.1 years. Both exceed the average menarcheal age in the USA even from the 1930s and 1940s (Berkey et al., 2000). It is likely that age at menarche in the UK varied from that of the USA since even into the 1950s the UK was suffering the after effects of the Second World War. Moreover, the Newcastle Thousand Families Study was started because of concern over the extremely high infant mortality rate in the city, which reflected the relatively poor living conditions for families in the area (Pearce et al., 2009) and would therefore impact age at maturation.

A study from Glasgow does show a drop of six months in the age of menarche among women from 1948-1968 (Okasha et al., 2001). Female students born between 1919 and 1952 were divided into quintiles [1919-1931, 1932-1936, 1937-1942, 1943-1946 and 1947-1952] and there was an average 10-day per

year drop. This drop could be the result of improving nutrition both through increasing intake for the poorest via rationing, and following the post-war period as conditions improved for all. However, the specific dietary information for this study population is unavailable to confirm this.

On the continent, a cohort of Swiss girls followed from 1950-1980 had an average age at menarche of 13.3 years (Heger et al., 2008). This is significantly older than menarcheal ages reported in other areas in a similar period (see table 4.3).

The youngest reported mean age at menarche from all the studies was 12 years in Egypt (Torres-Mejia et al., 2005) based on data from 4636 girls collected from 1998-1999. The nearest menarcheal ages were 12.16 in the USA (Biro et al., 2003) and 12.29 years in Greece (Papadimitriou et al., 2008), which had sample sizes of 1166 and 750 respectively.

Typically, environments of greater wealth and improved living conditions accelerate age at maturation, but as a lower middle-income country, Egypt is in stark contrast to the USA and UK (The World Bank, 2013). It seems counter-intuitive when we consider LHT that slightly poorer conditions nationally would result in a younger age at menarche, but this could be an indication of other cultural, or genetic factors in the Egyptian population that predisposes girls to a younger age at menarche. But it should be considered that although the sample is described as "nationally representative" the wealthiest girls in Egypt, where the disparity between the general population and the very affluent is extreme, could dramatically skew results.

While there are suitable longitudinal data to determine a continued downward trend in age at maturation in the USA, the same cannot be said for other areas. Many studies are cross-sectional rather than longitudinal and methodologically varied, which limits any conclusions we can draw from them with respect to a

secular trend. Studies that concentrate on one population over time will far better examine changes in maturation over time, and will be able to pinpoint aspects of their environment that could contribute to accelerated maturation in females. However, these studies do highlight the degree of variation in developmental age between different populations, which may reflect the varied ecological and lifestyle conditions around the world.

Catch-up growth

A low birth weight and BMI above 16.3 at age 8 years were associated with early menarche in a study of girls in western Australia who were tracked longitudinally from 10 weeks gestation until 13 years (Sloboda et al., 2007). Similarly, in a group of 14 year old Polish girls, those born SGA were more likely to experience menarche by age 14 compared with girls born normal, or above normal weight (Koziel and Jankowska, 2002). The same study also found that a higher BMI during childhood and at age 14 increased the likelihood of menarche prior to 14, which suggests the two factors may be related such that increased weight following SGA accelerated age at maturation. A similar effect has been found after weight gain in very early childhood; girls with reduced birth weight and rapid weight gain before 2 years were younger at the point of the pubertal growth spurt and experienced earlier menarche than girls born AGA. This was independent of mid-childhood body composition (Karaolis-Danckert et al., 2009). Terry et al. (2009) found a similar effect where weight gain following SGA occurred as early as 4 months. These studies add to an expanding body of literature that highlights the risk of early maturation for girls who experience pronounced catch-up growth. However, since the mechanisms for pubertal onset are much more related to hyperandrogenism in this group it does not necessarily represent the effect of overweight for girls born AGA.

Menarche, overweight and ethnicity

Ten studies looked at differences in maturation among different ethnic groups, but only two were based outside the USA. All eight studies from the USA highlight accelerated maturation in African-American girls (Adair and Gordon-Larsen 2001; Anderson et al., 2003; Anderson and Must 2005; Britton et al. 2004;

Freedman et al., 2003; Himes et al., 2004; Lee et al., 2007; Salsberry et al., 2009). They are followed by earlier maturation in Hispanic and Asian girls in the USA (Novotny et al., 2006), with white American girls thought to be the slowest to reach maturity. In contrast, Kaplowitz et al. (2001) and Freedman et al. (2003) found the association between higher BMI and early maturation to be stronger in white females. Additionally, in Freedman's study Hispanic girls were larger but did not develop more quickly, while Kaplowitz et al. (2001) saw earlier adrenarche in early-maturing white girls as opposed to African-American girls.

While Kaplowitz et al. (2001) found a stronger association between overweight and accelerated maturation in white girls, overall it was found that African-American girls mature earlier (2001). This could be an indication that more African-American girls in the general population are overweight compared with white girls or it could be a bias in the sample that selected more overweight African-American girls than is representative. It is more likely the former since there is evidence from NHANES that African American girls were, on average, heavier than their white peers (Flegal et al., 2010).

However, these results may be skewed based on population bias. Lee et al. (2007) found a strong correlation between African-American ethnicity and early maturation despite the low number of black girls in the cohort (n=46/354). Other studies were confounded by the type of cohort, where the girls who were maturing earlier were in fact slightly taller and older on average (Britton et al., 2004). In Anderson and Must (2005), there was a strong influence of the "other" group, which, when removed to leave only black and white, reduced the effect to which ethnicity affected maturational timing. A study in Hawaii by Novotny et al. (2003) found that SE Asian girls were more likely than white girls or Pacific Islanders to mature early.

Torres-Mejia et al. (2005) is the only comparative study included in this review. It compared girls in Mexico and Egypt and found overweight to be a significant factor in early maturation for both populations. Mexican girls matured earlier,

but being overweight had a stronger influence on early maturation in Egyptian girls. However, comparing girls in very different backgrounds who experience a vastly different lifestyle – and different genetic influences on maturation- makes it very difficult to separate the causative factors from other influences. It would probably be more suitable to consider the effects of ethnicity within the same environment, as in the USA studies. Understanding the role of ethnicity in the context of changing age at puberty is important for recognising risk factors of early maturation in particular ethnic groups, and especially in migrant populations as a result of phenotypic plasticity in maturation in response to catch-up growth.

When understanding the role of ethnicity it is important to note that population differences in maturation timing are also strongly tied to genetics. It is well established that age at menarche is in part influenced by your mother's age at menarche, but this is also somewhat true on a population level, and could explain some of the differences in average age at menarche, which have in the past been sometimes explained by altitude or climate.

On the individual level, the gene locus *LIN28B* was found to be significantly associated with variation in pubertal age in a sample of over 16,000 women (Ong et al., 2009). It is specifically associated with age at menarche and earlier breast development (Ibid). A number of reviews have found *LIN28B* to be closely associated with both growth and age at menarche, suggesting a modulating role in the overall process of puberty (Gajdos et al., 2010; Dauber and Hirschorn, 2011). The variation in the timing and appearance of puberty on the *population* level may be explained to some degree by global genetic ancestry (Gajdos et al., 2010). Although it cannot account for all of the differences observed among ethnic groups (ibid), common ancestry may be useful in understanding how age at puberty is similar among some groups and vastly different among others.

Ethnicity, environment and pubertal maturation

Not only is it important to recognise the effects of different environments on maturation, but also the impact a changing environment during childhood can have on maturation.

Ethnicity is known to affect age at maturation in the migrant context. There is an extensive literature on the effect of accelerated maturation in girls who are adopted from one country and mature in another. For example Virdis et al. (1998) found that in girls adopted from developing countries to Italy that were referred for signs of precocious puberty, significant catch-up growth and all-around improved conditions for physical and social development triggered pubertal processes earlier than is typical for Italian-born peers. Similarly, a Danish study found that girls and boys adopted from developing countries were 10 to 20 times more likely to develop precocious puberty, and late adoption was a significant risk factor (Teilmann et al., 2006).

Additionally, Nunez-de-la Mora et al. (2007) carried out a migrant study of Bangladeshis in the UK to show that moving to a country with significantly different conditions, like reduced exposure to pathogens during childhood, significantly increases adult steroid hormone levels in girls who were born elsewhere. The younger the Bangladeshi girls were when they moved to the UK, the earlier their age at menarche (Nunez-de-la Mora et al., 2007).

Skeletal growth and development

He and Karlberg (2001) considered the interaction between weight and height preceding puberty and found that early-maturing girls who had a higher BMI at age 8 tended to be taller preceding puberty but shorter following puberty compared with peers. He and Karlberg explain these findings as a trade-off whereby the oestrogen surges associated with puberty that occur younger in early maturers, cause epiphyseal fusion in the long bones sooner, resulting in reduced height growth. Moreover, girls who enter puberty younger tend to

proceed through puberty quicker than late-maturing peers (e.g. Apter and Vihko, 1984). So, regardless of increased height relative to peers preceding puberty, the *duration* of height growth during puberty is shortened, reducing final stature.

Ellison (1982) highlighted not only the higher degree to which skeletal height correlates with variance in menarcheal age compared with fatness, but also that natural selection has acted to synchronise menarche with pelvic maturation. This synchronisation ensures that, should pregnancy occur at or around the point of maturation, the individual has pelvic dimensions big enough for the safe passage of an infant through the birth canal during labour (ibid).

The reduction in height of early-maturing girls compared with peers may compromise the obstetric process, but since fatness in early-maturing girls is associated with low SHBG and high free oestrogen it is likely that girls hip dimensions may mature as normal. It would be necessary to measure hip dimensions in early-maturing girls in order to fully understand this relationship.

Synchronicity of maturation

Although overweight and obesity seem likely to decrease age at puberty in girls, they have a much greater impact on the likelihood of asynchronous pubertal development, where breast and pubic hair development proceed separately (Schubert et al., 2005; Biro et al., 2003; Denzer et al., 2007; Britton et al., 2004 and Christensen et al. 2010a). The effect may be greatest in some groups versus others: Schubert et al. (2005) found that non-white girls had a higher BMI when breast stage was more advanced. Where overweight girls present with asynchrony it is more likely to manifest as thelarche first (Biro et al., 2003; Britton et al., 2004; Denzer et al., 2007; Schubert et al., 2005). Three papers referring to this issue are from the USA, with one paper from Germany (Denzer et al., 2007) and another from the UK (Christensen et al., 2010a). The overwhelming argument from these papers is that there is a greater degree of

asynchrony in the development of secondary sexual characteristics among females who are overweight.

If, as these five papers suggest, thelarche is beginning earlier in heavier girls, but there is little evidence for a great decline in age at menarche over the same period, the heaviest girls are at risk of an extended period of *pre*-menarcheal maturation. This extended maturational stage could have implications for both psychosocial development and for the incidence of adult-onset cancers, which are already closely linked to early developers (see Ellison 1998 and Golub, 2008).

Considering the evidence for an earlier onset of pubarche in girls born SGA who experience significant catch-up growth (discussed above), and the influence of overweight on early breast development in girls not born SGA, these results indicate that *two separate mechanisms* may be involved with the onset of asynchronous pubertal development in girls, and that they could be sensitive to both prenatal growth and overall childhood energy balance. This observation moves us away from the classic Tanner model of maturation. Further longitudinal studies of early breast development in AGA girls may elucidate those factors that may be interacting with weight status to cause this effect.

Body composition

Literature in the search also highlighted the possible role of patterned fat deposition and overall body composition on age at maturation, although there was little consensus on the location of extra fat deposits that are linked with early maturation. Polish girls age 8-15 from 1961-1972 who showed high central adiposity were more likely to mature early relative to peers (Koziel and Malina, 2005), whereas gluteofemoral fat -fat which lies around the hips and thighs- is significantly associated with early maturation in American girls in a cross-sectional analysis of the NHANES III dataset (Lassek and Gaulin, 2007). Lassek and Gaulin found that as long as body fat was situated around the hips instead of

on the extremities, girls were more prone to early maturation. These findings relate to normal weight girls as well as girls classed as overweight (Ibid).

These findings may be explained by birth weight and weight gain during early childhood. Girls born SGA who experience catch-up growth during early childhood are at risk of high levels of visceral fat, which is typically associated with an android body shape (high central adiposity) (Ibanez et al., 2008a; 2008b), even in the absence of obesity. Moreover, menarche tends to be advanced in girls born SGA (Ibanez and Zegher, 2006), which indicates the susceptibility of SGA girls with an android body shape to early maturation even in the absence of prolonged weight gain after the initial catch-up period. Girls born AGA who are therefore less likely to show an android fat distribution in favour of gynoid are at risk of early menarche as the result of total fat mass. Therefore, it is possible that the risk of early maturation may be differentially associated with catch-up growth following SGA, and total fat mass in the Polish and USA sample populations respectively.

We already know that a gynoid body shape is protective against syndrome X and cardiovascular disease (CVD) in adulthood (Ibanez et al., 2000; 2008a; 2008b). Specifically, gynoid fat in relation to total fat mass is protective against CVD and metabolic co-morbidities (Wiklund et al., 2008; Manolopoulos et al., 2010) as the result of a protective lipid and glucose profile and the storage of fatty acids (Manolopoulos et al., 2010). But the risks for SGA girls with high visceral fat and an android body fat distribution in the absence of obesity highlight the possibility for a protective effect of gynoid body shape among girls born AGA who are not overweight.

In order to understand definitively whether fat patterning plays a mechanistic role in determining age at maturation we would have to take a much broader look at differences in body shape across a greater number of populations, particularly since in addition to childhood growth and nutrition heritable characteristics play a significant role in determining body shape.

Dietary quality and composition

Diets high in both fat and animal proteins were found to be associated with an earlier age at maturation (Berkey et al., 2000; Britton et al., 2004), and in particular with accelerated breast development (Britton et al., 2004). Additionally, Novotny et al. (2003) found that formula-fed infants are more likely to experience earlier menarche than breast-fed infants. Chatterjee et al. (2009) found the reverse in the absence of animal fats and proteins. They found evidence of a delay in the development of secondary sexual characteristics in Jain girls from Jabalpur, India who ate a solely vegetarian diet.

These results indicate that both fats and animal proteins are specifically contributing to increased fat mass that is implicated in earlier maturation in females, and an increased reliance on formula for infants could have a similar effect since it is so energy-dense compared with breast milk (Dunger et al., 2005). Moreover, increasing energy intake in the form of fats and proteins during critical windows of development from early childhood could significantly increase the chances of early pubertal onset.

The neuroendocrine control of puberty

Hormones play a pivotal role in the orchestration of puberty and evidence from this review suggests that overweight results in a range of hormonal responses. The pulsatile frequency of luteinising hormone (LH) shows a marked change from low to high across puberty in obese girls, compared with the "normal" pattern of puberty, characterised by high night time and low daytime LH frequency early in puberty and a more constant pulse frequency in late puberty (Ibid). Obesity during early and pre-puberty is associated with reduced LH secretion and reduced nocturnal changes in LH amplitude compared with non-obese girls. The latter also show marked differences between nocturnal and diurnal LH concentration (McCartney et al., 2009). Obesity later in puberty (at Tanner stages 3 onwards) is characterised by high LH frequency (Ibid). This is corroborated by Bordini et al. (2009) who similarly found decreased nighttime LH production in pre-menarcheal pubertal girls above the 85th percentile for weight, compared with normal weight peers. Both studies suggest that increased

adiposity may suppress the HPG axis since LH is central in the stimulation of oestrogen production in the ovary.

Aside from LH, obesity is also associated with increased levels of the pre-adolescent hormone dehydroepiandosterone sulphate (DHEAS) (Baer et al., 2007; Denzer et al., 2007), higher levels of circulating steroid hormones (L'Allemand et al., 2002; Baer et al., 2007) and lower sex hormone- binding globulin (SHBG) (Baer et al., 2007; Denzer et al., 2007). Finally, Lassek and Gaulin (2007) found a significant increase in leptin levels for every 1cm increase in hip circumference in the third NHANES survey, which increased the odds of menarche by around one quarter.

These findings highlight the plasticity of human female puberty. There is a great deal of evidence for a range of ovarian function under energetic stress and as a result of underweight (Ellison et al., 1993; Panter-Brick et al., 1993; Jasienska and Ellison, 2004). From an energetic perspective it would seem logical that an increase in energy intake increases the portion of energy that can be expended on hormone production.

Conclusions

Although not universal, there is good evidence for a further reduction in the age at puberty for girls in the USA, and more specifically, that the average age at menarche is still falling. It is likely that these changes are a response to the increase in overweight and obesity and changing diets. This review discusses evidence of earlier age at pubertal onset in a number of regions, but lacks the longitudinal data in these areas to make strong conclusions about the influence of overweight on pubertal development under varied ecological and lifestyle conditions.

However, the data do suggest that there may be *two separate pathways to puberty* emerging. The first, via pubarche, is most common among girls born SGA who have significant catch-up growth during childhood. The second, via thelarche, is a greater risk for girls born AGA who are overweight during

childhood. Both sets of girls may respond to high fat diets at specific points during childhood. A number of studies highlight particular periods during childhood that are significantly related to an earlier onset of puberty among females. These periods could represent critical growth windows, which are especially sensitive to diet and lifestyle for future maturational trajectories.

Both of these pubertal pathways indicate a shift away from the typical Tanner model of puberty where the time between thelarche and pubarche is very short. A greater degree of asynchrony in thelarche and pubarche in the initial stages of puberty results in a prolonged period of pre-menarcheal pubertal development. It is unclear, however, whether this prolongs pubertal development overall. Asynchronous development also seems to be most significant in certain groups. For example, non-white, overweight girls are most at risk.

While this review collates the known effects of overweight and obesity on female pubertal maturation, it does not elucidate the mechanisms behind these effects. The monitoring effect of leptin may play a permissive role in the onset of puberty, probably tracking long-, and short-term energy balance, but it is unlikely to be the only hormonal signal involved in this shift of maturational age. If, as it appears, heavier girls are at risk of earlier maturation, then understanding these mechanisms is vital. Younger age at puberty is linked with early sexual experience, a host of detrimental psychosocial conditions as well as elevated health risks in later life. By understanding fully what puts girls at risk of early maturation we can work to reduce these risks. This focus must be widened

to understand longitudinally how these changes may affect girls on a global scale.

Chapter Five: UK trends in age at menarche and age at pubertal onset, 1948-2005

Introduction

As is clear from the previous chapter, a number of factors are working to change the age at which girls go through pubertal maturation. There is mixed evidence from different populations in the developed world, but strong trends for a decreasing age at menarche and decreasing age at pubertal onset have been shown in the USA (Anderson et al., 2003; Anderson and Must, 2005). The evidence for a similar shift towards earlier menarche and earlier age at pubertal onset in the UK is mixed (Berkey et al, 2000; Okasha et al., 2001). However, given the associations between early maturation and later risky sexual behaviours in adolescence (Deardorff et al., 2005) and higher rates of reproductive cancers in adulthood (Jasienska and Thune, 2001) it is imperative to determine if there is a trend for earlier menarche and earlier pubertal onset in the UK. By understanding the risk factors and growth patterns associated with either an early maturational strategy or early age at menarche then it might be possible to mitigate the negative effects for girls in later life. This might be either focusing on prenatal and neonatal growth, and growth during mid-childhood in order to monitor girls at risk of early menarche; or to assess environmental exposures that could be putting girls at risk of earlier pubertal onset. By highlighting childhood risk factors or by ensuring girls who fall into early pubertal onset or early menarche categories receive appropriate care it might be possible to mitigate negative health outcomes.

In order to determine evidence for a downward trend in age at puberty in girls in the UK I have sought cohort data from longitudinal datasets, which cover the span of time for which risky exposures -particularly overweight, obesity, low activity levels and exposure to synthetic compounds- have increased in the UK. Data cover the periods 1948 (when the Harpenden Children's Study began) to 2005 (when girls in the Avon Longitudinal Study of Parents and Children turned 16). Over that time there has also been a great deal of social and lifestyle change

that could influence maturation since environmental exposures of all kinds are likely to have some mediating effect on the feedback of conditions to the CNS and HPO axis, which are central in the role of pubertal onset. Some of these important factors are:

Health policy

Lots of changes in health policy took place between 1948 and 2005, not only with the introduction of the NHS in 1948, but also in public perceptions of health, long-term approaches to health and the increasing availability of antibiotics (Wadsworth et al., 2003b). Many people were successfully treated for diseases that had historically been killers, particularly among children, and even more so for families in overcrowded accommodations who had higher exposures to life-threatening respiratory infections (ibid).

Improvements in public health are thought to be the most significant factor responsible for the secular trend in age at menarche from 1830 to around 1960 noted by Tanner (1981). Since children were already in a position to experience better growth as sanitation had improved with the advent of the industrial revolution, could they also then mature younger as they were introduced to social change and excess over the latter part of the 20th century?

Food and obesity

In the post-war period, food and diet were a concern only in that there were still shortages across Europe. Britain didn't completely end rationing until 1954 (Wadsworth et al., 2003). Many jobs were still manual and children were more physically active than today (ibid). However, in the post-war boom and the optimism surrounding change and progress diets changed. What resulted is a level of overweight and obesity on epidemic levels in the UK.

So great is the concern over obesity in the UK populations that we now have a National Obesity Forum (NOF) and a National Obesity Observatory (NOO), and special hospital wards built to cater for the heaviest patients. Obesity has increased steadily over the last 30 years specifically (www.noo.org.uk), as the people in the UK started eating more saturated and hydrogenated fats, more

refined sugars from snack foods and sugary cereals, and rely more on processed foods than traditional home cooking. In addition to eating more there is also an abundance of obesogenic chemicals that have become part of our everyday exposures. These chemicals make it much easier for the body to store the excess fats we are eating (Grun and Blumberg, 2007; 2009).

Sedentary behaviours and play

Another social change is the shift away from manual work and skilled labour to computer-based jobs. The advent of technology has also put generations of children in front of computers, gadgets and games consoles, rather than playing in active sports and games. Supporting that is the change in parents' attitudes. With increased street crime and risk to vulnerable groups like children, the decline of the community and the numbers of cars on the streets, many parents encourage their children to play within the home. Whether this is a large house or high-rise flats, children nowadays are used to expending far less energy. They are encouraged in sedentary behaviour by parents who are uncomfortable allowing their children to play out of sight or where they feel they might be at risk (Davis and Jones, 1996).

School meals

Schools have somewhat played their part in changing childhood nutrition. After the introduction of Margaret Thatcher's market policies on school meals providers, children were getting a very different diet at school. The market competition introduced to the provision of school meals meant that home-cooked, healthy, nutritious meals were not a priority in the 1980s. There was no baseline nutritional value set for meals. Cooks were expected to use suppliers who could provide the cheapest food. Children were eating processed foods in schools, and daily milk allowances were stopped (Education Act, 1980).

Divorce and unmarried partnerships

Increasing numbers of one-parent families, unmarried partnerships and stepfamilies has changed the typical UK dynamic. The stress and uncertainty associated with the absence of fathers, the presence of stepfathers and changes in parental investment after siblings are born out of the new union are

associated with earlier maturation. Divorce rates in England and Wales showed a steady increase from 30,870 in 1950, peaking at 165,018 in 1993. That rate fell slightly through the remainder of the 1990s to 144,586 (ONS, 2011).

Poverty

Child poverty has been a governmental concern for a long time. In post-war Britain inequality rose with the vast change in industry. As semi- and unskilled labour forces diminished with the closure of many manufacturing hubs, coalmines, and traditional manufacturing industries, there were fewer opportunities for males with minimal qualifications. Girls growing up in households in the eighties may have been at greater risk of parental unemployment and financial hardship than the preceding generation. Those with more qualifications in skilled, technology-led jobs were seeing the benefits of the technological boom. International trade markets and a reliance on technology meant more inequality for wage earners (Dearden et al., 2003).

In the 90s we saw the introduction of the national minimum wage, which may have minimised the impact in the decline of manual work and public sector work (Dearden et al., 2003). Poverty in the 80s and onwards was nothing like the scale seen in post-war Britain, particularly in Newcastle, which was the focus of much concern since the number of deaths in infancy was considered very high in the area (Pearce et al., 2009).

Housing

The late nineteen forties and early nineteen fifties was a period when social housing was just beginning (Smith and Ferri, 2003). For example, in Newcastle there were a number of pre-fabricated houses built (Miller et al., 1960). It was fairly common to have no access to a bathroom in a family dwelling (Smith and Ferri, 2003). Over the latter part of the 20th century and into the 21st century these conditions have improved enormously. It is now incredibly rare for families to live in dwellings without indoor water facilities, or for children to grow up in overcrowded environments.

Background

The Harpenden Children's Study

The Harpenden growth study began in 1948 and forms the basis of modern studies of pubertal development. Professor James Tanner and Reginald Whitehouse took both anthropometric and pubertal scale measures of a group of children in the Harpenden Children's Home for over two decades until 1975. Each child was measured, on average, every six months during the pubertal period, and other measurements were also made during early childhood. Pubertal measures as a reference scale developed during this process, which led to the development of a set of five discrete stages of pubertal maturation commonly known as the Tanner-Whitehouse scale. Some children were measured for a significant portion of their childhood, others over a few months or years.

Participants of the study remember being measured at regular intervals of around three to six months. Tanner and his colleagues would spend around two hours weighing, measuring and examining each child (Howard, 2007). For younger children this involved anthropometric measures only. For the older children they were examined for signs of puberty, and data was recorded on their stage of development. For girls, their age at menarche was recorded at the first examination post-menarche.

Participants comment that children in the study were likely experiencing a diet in the 1960s that was similar to that of children in the 1950s (Howard, 2007), because all of their food and amenities came from a finite government budget. Indeed, it would be plausible that the Harpenden children did not represent closely enough the population as a whole, and were therefore an unreliable sample from which to construct growth curves and maturational norms, if they were on a more restricted diet than the general population as the result of their reliance on government and social services. However, James Tanner believed strongly that all of the children looked well nourished, were well cared for and were in good health when they were examined. Many of the children joined the

Harpenden Children's Home between the ages of three and six, and it is likely much of their catch up growth took place in that time and they proceeded through comparably normal growth and sexual maturation (Tanner, personal communication via Nöel Cameron, 2009).

The British Cohort Study 1958 (BCS58)

Similarly to the beginnings of the Thousand Families Study, the British Cohort Study -originally the National Child Development Study (NCDS) - began over concerns about UK national perinatal mortality. In particular, the rate of stillbirth was high enough to cause considerable disquiet (Power and Elliott, 2006). The study was also a way to evaluate maternity care after ten years of the NHS (Wadsworth et al., 2003a).

The role of the study was to understand or pinpoint possible contributing factors, of maternal origin and from gestation and early infancy, which might help to understand perinatal mortality, specifically stillbirth and neonatal death (Ibid). The study recruited 17,416 infants born in one week in 1958 in England, Scotland and Wales, and recorded maternal variables, information on the pregnancy and birth of the infant, as well as perinatal anthropometrics, living conditions and social circumstances of the family. The study was not initially intended to be longitudinal, but the infants and families were traced for further sweeps at age seven, 11, 16, 20, 23, 33, 42, 45, and 46 (Ibid). This study concerns data from the initial data sweep and the three successive sweeps up to age 16: at birth (1958), age seven (1965), age 11 (1969) and age 16 (1974). The latter three sweeps contains data from the participants, their parents, participants' school tests and a medical exam (ibid).

Data on children came from questionnaires given to parents when the cohort member was born, from medical examinations at age 7 and 11, and primarily from the participant in adulthood. Medical data from examinations was mostly obtained from school doctors, and other health information from the parents (Power and Elliott, 2006).

Children in the study were more likely to come from poorer homes than a contemporary population. That is, they often had poor amenities in the home. However, they were less likely to be obese than children currently born in the UK- this was one of the first cohorts to show an association between earlier adiposity and advanced maturation-, and more likely to live with both biological parents. Rates of divorce were much lower in 1958, which contributes to this common family scenario seen in the dataset (Power and Elliott, 2006).

The cohort is not as ethnically diverse as a contemporary population in the UK, but is representative of the time. Immigrants who matched the birth criteria were recruited into the study throughout various data sweeps (Power and Elliott, 2006).

The British Cohort Study 1970 (BCS70)

Originally named the British Births Survey (BBS), The British Cohort Study 1970 (BCS70) began following the success of the 1958 National Child Development Study. The study gathered nationwide birth information for 17,198 births (live and stillbirth) in the week 5th-11th April 1970 (The 1970 Birth Cohort, Institute of Child Health). When the cohort members were three years of age the study was moved to the Department of Child Health, Bristol. It was moved again at 16 years to the International Centre for Child Studies. In 1991 the cohort was taken under the management of the Social Statistics Research Unit, and in 1998 by the Centre for Longitudinal studies, where it remains (Elliott and Shepherd, 2006). It is perhaps this peripatetic nature that could be responsible for the ever-expanding focus of the study.

A number of data sweeps took place to gather growth and development data, school examinations and arithmetic tests, economic and social data, and medical examination data. Full cohort sweeps took place at 5 years, 10 years, 16 years, 26 years, 30 years and 34 years. Sub-sample data were gathered at 22 and 42 months of age to cover the important developmental period up to 5 years of age.

Each successive sweep added children who now resided within the UK, but may have been born elsewhere, who were born in the target week 5th-11th April, 1970. The focus widened across the sweeps from strictly medical-related data to include more social and economic factors describing lifestyle and education (ibid). Immigrants who were born in the target week and moved to Britain were traced through schools (Elliott and Shepherd 2006). Much like the BCS58, BCS70 does not have nationally representative ethnic diversity of 1970.

The data sweeps of interest in these analyses are the birth data and the three subsequent sweeps up to age 16, as well as data from the 22- and 42-month subsamples. Data at birth were collected from midwife questionnaires, and subsequently from clinical records (Elliott and Shepherd, 2006). In order to ensure that as many births as possible were recorded during the one specified week the British Medical Association had a meeting of all the Chief Medical Officers, the Directors-General of the Army Medical Service and the Medical Services Air Force were contacted respectively, as was the head of the Prison Medical Service. Awareness of the survey was raised to general practitioners and midwives through the professional services and industry journals. All but a few domiciliary births (home births) were recorded (The 1970 birth cohort, Institute of Child Health).

The Avon Longitudinal Study of Parents and Children (ALSPAC)

ALSPAC (also known as the Children of the 90s study) is a longitudinal birth cohort study based in the county of Avon, UK. The study aims to understand the effects of health and social factors on health, development and social outcomes throughout the life of the individual. Although the study may not be 100% nationally representative, the concentration of people around the study centre no doubt aided effective follow-up.

ALSPAC began as a response to a WHO meeting in Moscow that pointed out the necessity for longitudinal studies that aim to understand modifiable health outcomes in children (Boyd et al., 2012). ALSPAC recruited around 14,000

pregnant women who were due to give birth between April 1991 and December 1992; initial recruitment was 14,571 pregnancies. After other children were followed up who failed to take up the study initially, 14,701 children could be identified who were born during the above period and survived to at least 1 year of age. A 10% sample (children in focus) was chosen from the last 6 months of recruitment. They were tested in clinics at various intervals up to 5 years of age. Children of families who had moved out of the area were excluded from this sample.

The sample has a shortfall in ethnic minority mothers, and is under-representative of less affluent families. The families in the study were more likely to be owner-occupiers (79%), less likely to have one or more person per room (33.5%), and more likely to own a car (90.8%), than the national average for 1991 (University of Bristol, 2012).

Girls' pubertal development was assessed annually over nine years by completion of questionnaires by the mother, or both mother and daughter (8-13 years), and finally by the daughter alone 14.5-17 years). Information was collected on age at menarche, frequency of periods, and length of periods. Tanner stages were presented as pictures with descriptions alongside them for self-report with no clinical assessment (Christensen et al., 2010).

Questionnaires on pregnancy, labour, childhood health and nutrition, education, social factors, adolescence, and the family were collected throughout the study. Participants continue to provide information to the study (Golding et al., 2001; Golding, 2004).

Subjects and methodologies

The Harpenden Children's Study data were given to me by Professor Noel Cameron (Loughborough University, School of Sport, Exercise and Health

Sciences), who had inherited the data directly from Professor James M. Tanner of the original study. The data had been stored in an unreadable format from a statistics package that is no longer available. In order to extract the data it was opened in TextEdit for Mac (2008), which is equivalent to Notepad on a Windows™ computer. This produced lists of numbers, which could then be interpreted based on Tanner and Whitehouse's published notes. The data were aligned with measurements listed in Growth at Adolescence 2nd Edition (1962:240) with the assistance of Prof. Cameron.

Dr. Jonathon Carter was responsible for writing a source code to align the correct columns of information with subject identification numbers and then moving these data into an Excel spreadsheet. The variables retained and transferred to SPSS for the purpose of this study are listed in appendix 1. For measurements of height and weight data were retained for the first measurement taken for each year of age.

Data were analysed for 217 girls from the study, measured at various periods throughout childhood during periods they were resident in the Harpenden Children's Home. These data contained breast and pubic stage, as well as an indicator for menarche. Girls were listed at a discrete Tanner stage each time they were measured.

In order to estimate when thelarche and puberty occurred, it was necessary to determine for each girl at what point they went from Tanner Stage 1 to 2. The midpoint between measurements was considered the point at onset, since the exact age was not available and taking either the measurement before or directly after the change was detected would bias the data in one direction to a greater degree than the midpoint between the two. For age at menarche the mid-point between 1 (non menarcheal) and 2 (menarcheal) was recorded as age at menarche. This cohort contains pubertal data on girls from the 1948-1975.

The British Cohort Study 1958 (BCS58) data are available at the Economic and Social Data Source (ESDS). The data were downloaded from the online source in SPSS format into SPSS version 19 for statistical analyses. The variables retained and transferred to SPSS for the purpose of this study are listed in appendix 1. These variables came from a number of original files. They were downloaded into SPSS, and the required variables were exported to an Excel spreadsheet. Each successive variable from a new SPSS source was matched by ID number to align the entries.

This sample of the BCS58 contains data on 8959 girls. This includes both girls who were enrolled at birth and those girls who were traced through schools when they moved into the area and met the birth date criteria of the study.

Data are available for birth weight, as well as measures of height and weight at age 7, 11 and 16. Data on social class, ethnicity and members of the family were collected at birth.

Girls aged 11 were examined for breast and pubic hair development and were determined as "early maturation", "2", "3", "4", or "late maturation". The original notes accompanying the questionnaires are not currently traceable, so it is difficult to understand how these descriptions might tally with Tanner stages of pubertal development. For this study "early maturation" has been amalgamated with "2", which suggests that both of these descriptions are measures of early development. Girls were classed as "unable to assess", which may have been the proxy measure for Tanner breast stage 1. Similarly, girls described as "late maturation" have been grouped with "4" which, following Tanner stages, indicates advanced breast development before the adult stage. Girls described as "3" have been classed as Tanner stage 3.

Age at menarche was recorded retrospectively at age 16. At age 16 girls were also examined again for breast and pubic hair development. In this sweep they

were categorised into “absent”, for absence of signs of maturation, “intermediate”, which, in the absence of the original guidance notes has been taken to mean the intermediate stages of development between child and adult (Tanner stages 2, 3 or 4), or “adult”, which would correspond to B5 for adult, fully mature stage breast development and PH5 for adult pubic hair development. This cohort contains pubertal data from girls from 1969-1974

Originally named the British Births Survey (BBS), *The British Cohort Study 1970 (BCS70)* The data from the BCS70 are available at the Economic and Social Data Source (ESDS). The data were downloaded from the online source in SPSS format into SPSS version 19 for statistical analyses. The variables retained and transferred to SPSS for the purpose of this study are listed in appendix 1. These variables came from a number of original files. They were downloaded into SPSS, and the required variables were exported to an Excel spreadsheet. Each successive variable from a new SPSS source was matched by ID number to align the entries.

Subjects were 8279 girls from the BCS70. Pubertal data was described at age 10 and 16. At age 10, any indication of pubertal onset was recorded by clinical examination. The nature of this event was recorded as breast development, pubic hair development, axillary hair development, menarche, or other. Age at menarche was retrospectively recorded at clinical examination age 16. Heights and weights were recorded by clinical examination. Parental questionnaires returned information about ethnicity, home life and familial relationships. This cohort contains girls’ pubertal data from 1980-1986.

Avon Longitudinal Study of Parents and Children (ALSPAC), 1991

Due to limits on access to the study, namely an embargo on early childhood data used by other research groups, published data on the ALSPAC dataset is reported from secondary sources. These data, however, indicate pubertal status of girls in

the study, as well as social and health factors that may contribute to pubertal outcomes.

Data were obtained from 3,938 girls (Christensen et al., 2010a). Girls were categorised into pubertal initiation pathway. Those with signs of breast development first were in the thelarche pathway, those with pubic hair growth first in the pubarche pathway, and girls whose initiation pathway was undeterminable were in the synchronous developmental pathway (Christensen et al., 2010a; 2010b). This published data contains girls' pubertal information from 1999-2005.

Handling longitudinal data

This Chapter uses data from longitudinal studies of growth and health from the 1940s through to the beginning of the new millennium. Although the studies themselves are longitudinal the data extracted for use in this thesis represents cross-sections of information since it is concerned with measures at specific points in time. Therefore, methods designed specifically for the analysis of longitudinal data are inappropriate here (Singer, 2003 Agresti and Finlay, 2008)

The data were uploaded to an SPSS (version 19) data sheet for statistical analyses. In order to understand whether there is a trend over time I tested for the following outcome measures: Age at pubarche, age at thelarche, age at menarche, mean and median weight at pubarche, thelarche and menarche. Outliers were removed in SPSS by removing individuals whose first sign of puberty occurred before age 7 or after age 16.

Statistical methodologies:

Survival analysis, or time-to-event data, is often used in biomedical or clinical studies where the outcome measure is the time at which a particular event takes place (Yamaguchi, 1991). This type of study is particularly useful when data are

missing or censored. However, survival analysis requires a specific beginning point in addition to the end point of interest. For many of the individuals in these analyses no date of birth was available. When these points are censored you cannot make a valid estimate of the outcome. Instead, mean and median ages at thelarche, puberche, and menarche were calculated from the available data from each dataset and a number of other statistical methodologies were used to analyse the predictors of age at pubertal onset and age at menarche.

Independent samples T-tests were carried out to find a difference in the mean weights of girls who mature before the age of 13. Here a t-test specifically determines whether or not early-maturing girls are heavier over time than their later maturing peers. Those weights at ages found to influence this outcome were subsequently included in regression analyses.

Simple correlations were investigated between early life factors and age at pubertal onset and menarche in order to determine whether there was a relationship between factors of lifestyle and growth in early life, and pubertal onset. Those factors that were correlated with pubertal onset were subsequently included in regression analyses. Multiple linear and logistic regressions were then carried out in order to understand the relationships between factors that are associated with pubertal onset and age at menarche, and also to determine which factors could best predict the outcome measures.

In order to plot change in pubertal onset over time the results from each dataset were compared to determine change in mean and median ages at puberche, thelarche, and menarche. The strongest predictors of pubertal onset and age at menarche from each dataset were then compared to determine whether different influencing factors were acting to promote pubertal onset over time.

Results

The Harpenden Children's Study

Mean and median age at menarche was 13.13 and 13.17 respectively. Mean and median age at thelarche and pubarche was 11.15 and 11.19, and 11.48 and 11.61 respectively. Table 5.1 gives the anthropometric descriptive statistics for the girls in the Harpenden study, and table 5.2 gives the menarcheal descriptive statistics.

Age	Height (cm) Mean(S.E)/Median(Range)	Weight (kg) Mean(S.E)/Median(Range)	n=	% Reached menarche (n)
9	132.49(.59)/132.40(33.60)	28.45(.35)/28.60(21.00)	123	
10	138.24(.59)/138.40(31.80)	31.77(.40)/31.40(24.60)	122	
11	142.95(.63)/143.00(35.30)	35.43(.49)/35.40(29.30)	127	
12	149.10(.67)/149.10(38.90)	40.24(.59)/40.10(35.20)	122	
13	154.56(.60)/155.00(30.80)	45.70(.63)/45.60(36.50)	121	82.8
14	158.52(.59)/158.20(27.40)	50.46(.74)/49.75(41.30)	107 /108	96.0
15	160.14(.63)/160.20(27.60)	53.30(.89)/52.90(40.40)	84	
16	160.21(1.49)/162.05(74.10)	55.78(1.01)/54.30(34.40)	50/49	99.0
17	161.26(1.02)/162.40(26.30)	56.99(1.34)/56.00(35.60)	40	
18	162.47(1.33)/161.50(26.80)	58.63(1.67)/59.30(34.20)	27	

Table5.1. Harpenden cohort anthropometric descriptive statistics.

Table 5.2 Harpenden cohort menarcheal descriptive statistics.

Pubertal milestone	**n=**	**Mean(S.E)/Median(Range)**
Age at menarche (years)	99	13.13(.11)/13.17(8.34)
Age at thelarche (years)	114	11.15(.11)/11.19(5.84)
Age at pubarche (years)	109	11.48(.18)/11.61(6.13)

Independent-sample t-tests found that girls who reached menarche before age 13 were significantly heavier at age 9 ($t(60)=4.334$, $p<.001$), 10 ($t(66)=5.133$, $p<.001$), 11 ($t(82)=4.821$, $p<.001$) and 12 ($t(87)=5.568$, $p<.001$) Early maturing girls were also significantly taller at age 9 ($t(60)=3.497$, $p<.01$), 10(t(58.692)=3.881, p<.001), 11 ($t(82)=4.785$, $p<.001$) and 12 ($t(87)=5.288$, $p<.001$).

Weight at age 9 was significantly negatively correlated with age at breast development ($r=-.328$, $p<.01$). Independent-samples t-test found that weight at age 9 ($t(81)= 2.488$, $p<.05$), height at age 11 ($t(94)= 2.281$, $p<.05$), and weight at age 11 ($t(94)= 2.609$, $p<.05$), were significantly positively associated with an earlier age at thelarche, specifically age at thelarche before 11.15 years, which is the Tanner mean for B2. Additionally, weight age 9 ($t(76)= 2.533$, $p<.05$), weight at 10 ($t(85)= 2.052$, $p<.05$), weight at 11 ($t(95)= 2.963$, $p<.01$), and height at 11 ($t(95)= 3.057$, $p<.01$) were significantly positively associated with early pubarche (PH2 before age 11.69, Tanner's mean PH2).

Stepwise multiple linear regressions found that:

Height at age 11 was a significant predictor of age at menarche. Adjusted $R^2= .39$ (see table 5.3). Height at age 9, and height and weight at age 11 were significant predictors of age at thelarche. Adjusted $R^2= .36$ (see table 5.4). Height at age 9 and 11 are significant predictors of age at pubarche. Adjusted $R^2=.17$(see table 5.5).

Table 5.3. Stepwise multiple linear regression predicting age at menarche

Variable	Estimate (B and SE)
Intercept	27.070, 2.254***
Height age 11 (cm)	-.098, .016***

Adjusted R^2=.39. ****p*<.001.

Table 5.4.. Stepwise multiple linear regression predicting age at thelarche

Variable	Estimate (B and SE)
Intercept	10.105, 2.307***
Height age 9 (cm)	.221, .051***
Weight age 11 (kg)	-.091, .030**
Height age 11 (cm)	-.175, .050**

Adjusted R^2=.36. ***p*<.005, ****p*<.001.

Table 5.5. Stepwise multiple linear regression predicting age at pubarche

Variable	Estimate (B and SE)
Intercept	17.126, 2.653***
Height age 9 (cm)	.177, .062**
Height age 11 (cm)	-.203, .055***

Adjusted R^2=.17. ***p*<.005, ****p*<.001.

Multinomial logistic regression found no significant predictors of pubertal onset pathway (thelarche, pubarche or synchronous pubertal onset).

Discussion

These results do not exactly match those from Tanner's original publications regarding girls at the Harpenden Children's Home (Marhsall and Tanner, 1969). However, the dataset used here was in an unreadable, digital format for many years and it is impossible to know whether these are exactly the same individuals used in the original study, or whether a different sample of girls was analysed.

Both earlier age at pubertal onset and menarche are associated with higher weight status and greater height from age 9 until puberty. The relationship appears very linear, in that those girls who are growing bigger sooner (i.e. have a faster growth trajectory), are reaching puberty sooner. It is highly unlikely that girls in a children's home would easily become overweight since only a certain amount of food was available for each child within the allotted budget.

Multiple linear regressions found that height at age 11 is a significant predictor of age at menarche, age at thelarche and age at pubarche. Similarly, Height at 9 was significantly associated with pubertal onset. Weight at age 11 was independently associated with age at thelarche. It is interesting that in the regression model weight was not associated with age at menarche, and measures of height are more often predictors of age at pubertal onset in this cohort. However, given that girls in a children's home during this period were unlikely to be overweight (due to strict food budgets) it is perhaps understandable that other factors might be stronger predictors. As Ellison (1981, 1982) has discussed, variance in height reduces at menarche, so these results support the hypothesis that skeletal development is a strong predictor of age at menarche. These results also suggest that skeletal maturation may be a predictor of pubertal onset. Given that the onset of puberty leads towards menarche this could be evidence that variance in height is also reducing at pubertal onset.

It is interesting that Tanner determined that much catch-up growth had taken place for those children who many have been undernourished and small for their

age when they entered the home (Tanner, personal communication via Nöel Cameron, 2009). While this might mean that children were of comparable size to their peers at puberty, we know now that catch-up growth can have considerable impact on the progression through puberty. Girls who experience a lot of catch-up growth begin puberty via pubarche significantly more often than girls who are born at an appropriate weight for gestational age. Unfortunately, birth weight was not available for this dataset and very few girls were recorded at a consistent age before age 9 so it is impossible to understand how catch-up growth in infancy may have impacted on pubertal development in the Harpenden girls.

The British Cohort Study 1958 (BCS58)

Table 5.6 (overleaf) provides descriptive statistics of anthropometrics collected for girls in this sample. Figure 5.1 shows the distribution of age at menarche in the sample. Mean and median age at menarche were 12.72 (*SE*=.02) and 13.00 (range =7, *n*=4429). Eighty-four percent of girls showed signs of breast development at age 11, and 83% of girls had signs of pubic hair growth age 11. Of the girls with data on breast development age 11, 72% were at B2, 20% at B3, and 7% were B4. For pubic hair development, 78% were at PH2, 14% were at PH3, and 8% were at PH4. At age 16 only 12 girls showed no sign of breast development and 17 had no sign of pubic hair development.

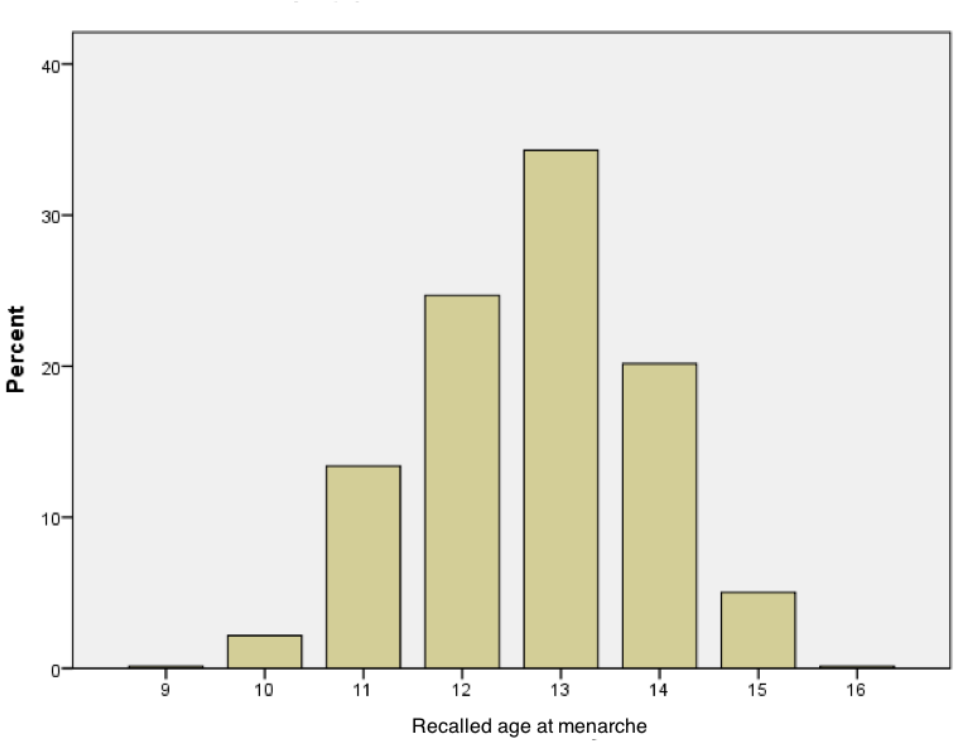

Figure 5.1 Distribution of discrete recalled age at menarche in the BCS58

Table 5.6. Descriptive statistics for BCS58

Age	**Height (cm)** **Mean(S.E)/Median(Range)**	**n=**	**Weight (kg)** **Mean(S.E)/Median(Range)**	**n=**	**% Reached thelarche (n)**	**% Reached pubarche (n)**	**% Reached menarche (n)**
Birth			3225(.22)/3231.8(3373.6) **(g)**	8143			
7	121.92(.07)/121.90(63.50)	6598	23.66(.05)/23.13(34.02)	5382			
11	144.73(.10)/144.80(76.20)	6194	37.19(.10)/35.83(69.40)	6165	83.7 (7450)	83.2 (7450)	
13							74.7 (1519)
14							94.8 (2412)
16	160.88(.09)/161.00(55.00)	5382	54.40(.12)/53.52(81.65)	5372	97.0 (5385)	94.4 (5208)	

Weight status in childhood did not correlate with pubertal onset. However, independent samples t-tests found that girls who reach menarche before 13 years of age are significantly heavier at both 7 years of age (t(2760.085$)$=13.45, p<.001) and 11 years of age (t(2802.399)=21.66, p<.001) than girls who reach menarche at age 13 and later. Age at menarche before age 13 is also associated with significantly greater weight gain between 7 and 11 years (15.91kg, versus 12.12kg) (t(2507.219)=20.59, P<.001).

Independent-samples t-tests found that menarche before age 13 was also associated with greater height at age 7 (t(3670)=10.69, p<.001) and 11(t(3048.320)=20.26, p<.001) compared with girls who reached menarche after age 13. Type of father figure present age 7 and 16, and social class of father had no effect on age at menarche.

Independent samples t-tests found no significant different in mean weight at age 7 or 11 of girls who did and did not show evidence of breast development at age 11. Additionally, there was no significant difference in mean weight at age 7 or 11 of girls who did and did not have evidence of pubic hair growth at age 11.

Independent one-way ANOVA found a significant linear relationship between breast stage at age 11 and age at menarche. Girls who are more developed age 11 have a significantly earlier age at menarche, F(2,1)=886.082, p<.001 (See figure 5.2). Additionally, the between-group interval in age at menarche decreases with higher breast stage age 11. The difference between girls at breast stages 2 and 3 is 0.92 years, and the difference in age at menarche between girls at breast stage 3 and 4 at 11 years is 0.60 years.

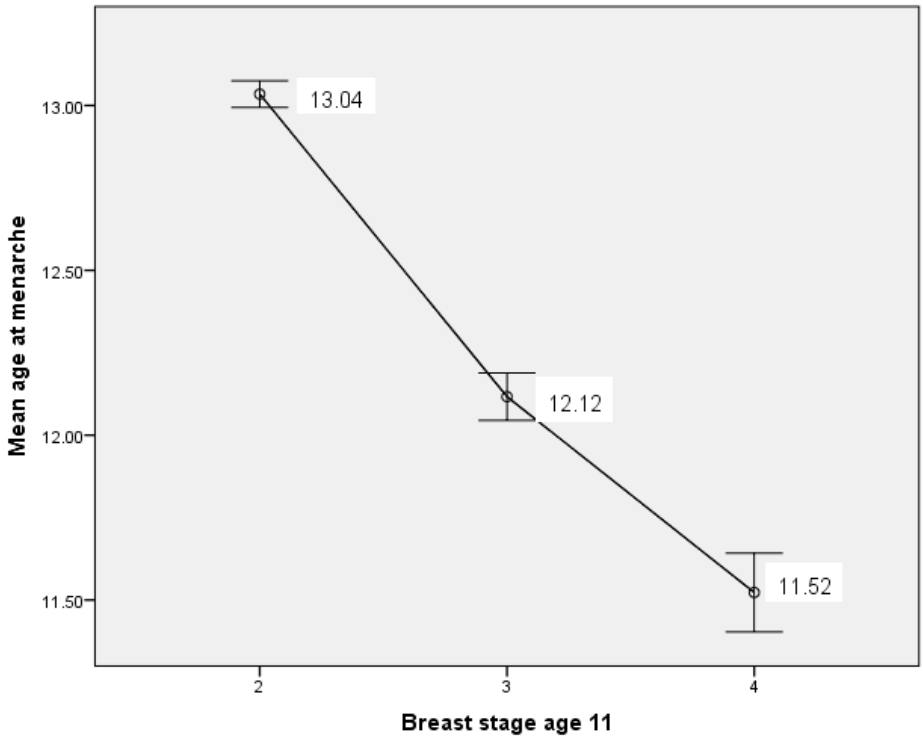

Figure 5.2. Mean age at menarche by breast stage at age 11

A stepwise multiple linear regression found that height at age 7, height at age 11, birth weight and weight at age 11 were significant predictors of age at menarche. Table 5.7 shows relevant beta coefficients and significance values for the model. Adjusted R^2=.24

Table 5.7. Stepwise multiple linear regression predicting age at menarche

Intercept	16.297, .454***
Weight age 11 (kg)	-.042, .003***
Height age 7 (M)	6.979, .534***
Height age 11 (M)	-7.637, .481***
Birth weight (Ozs)	.005, .001***

Adjusted R^2=.24 ***p<.001.

Multinomial logistic regression found that weight age 11 height age 7 and height age 11 were significant predictors of breast development. Table 5.8 shows relevant parameter estimates and significance values for the model. R^2=.28 (Cox & Snell), .36 (Nagelkerke). Model $X^2(8)$= 1687.350, p<.001.

Multinomial logistic regression found that weight age 7, weight age 11 height age 7 and height age 11 were significant predictors of pubic hair development. Table 5.9 shows relevant parameter estimates and significance values for the model. R^2=.22, (Cox & Snell), .30 (Nagelkerke). Model $X^2(8)$= 1278.027, p<.001. *** p<.001.

Table 5.8. Multinomial logistic regression predicting breast development age 11

	B (SE)	Lower	Odds Radio	Upper
2				
Intercept	18.772 (1.62)***			
Weight age 11 (kg)	-.165 (.01)***	.826	.847	.869
Height age 7 (M)	25.130 (2.10)***	1336626139.853	81964706004.259	5026246928781.451
Height age 11 (M)	-28.404 (1.70)***	1.657	4.618	1.287
3				
Intercept	7.120 (1.59)***			
Weight age 11 (kg)	-.041 (.01)***	.938	.960	.982
Height age 7 (M)	11.562 (2.04)***	1941.896	104991.724	5676545.348
Height age 11 (M)	-12.064 (1.62)***	2.414	5.763	.000

Note: R^2=.28 , (Cox & Snell), .36 (Nagelkerke). Model $X^2(8)$= 1687.350, p<.001. *** p<.001. 95% CI for odds ratio.

Table 5.9. Multinomial logistic regression predicting pubic hair development age 11

	B (SE)	Lower	Odds Radio	Upper
2				
Intercept	21.172 (1.56)***			
Weight age 7 (kg)	.073 (.03)***	1.024	1.076	1.130
Weight age 11 (kg)	-.108 (.01)***	.877	.898	.919
Height age 7 (M)	23.055 (2.03)***	191309216.081	10296008566.251	554117541056.057
Height age 11 (M)	-30.217 (1.68)***	7.534	2.782	2.040
3				
Intercept	7.958 (1.67)***			
Weight age 7 (kg)	.081 (.03)***	1.030	1.084	1.142
Weight age 11 (kg)	-.063 (.01)***	.916	.939	.963
Height age 7 (M)	9.050 (2.13)***	131.076	8517.438	553472.552
Height age 11 (M)	-11.885 (1.73)***	2.346	6.893	.000

Note: R^2=.22 , (Cox & Snell), .30 (Nagelkerke). Model $X^2(8)$= 1278.027, p<.001. *** p<.001. 95% CI for odds ratio.

Discussion

Mean age at menarche in this cohort is 12.72; however, age at menarche was collected as a discrete value, so it is more appropriate to consider the median age of 13. Age at menarche was also collected retrospectively at age 16, which does allow for some recall error (Koo and Rohan, 1997), but is not as great as the degree of error that results from adult recall many years after the event (Cooper,

2006). However, it does mean that the data are slightly right censored since some girls had no evidence of secondary sexual characteristics and were therefore unlikely to have reached menarche. Therefore, the true mean and median for age at menarche are likely to be slightly later.

Birth weight, and greater height at age 7 and 11, as well as higher weight at age 11 were all significant predictors of age at menarche (R^2=24.3). Although weight at age 7 did not significantly contribute to the model, it is clear that girls who mature earlier are heavier and taller than their peers by age 11. However, those girls who reach menarche before age 13 are heavier than their later-maturing peers at both age 7 and 11, and experience greater mean weight gain between age 7 and 11. This suggests that girls reaching menarche earlier have a faster trajectory of growth between age 7 and 11. Moreover, this indicates that environmental tracking by the CNS from age 7 might influence the maturation of girls who reach menarche before age 13. Girls could be tracking the environment in order to best apportion available energy.

Independent-samples t-tests did not find any association between height and weight, and the likelihood of pubertal onset by age 11. However, height and weight age 7 and 11 did significantly contribute to the stage of breast and pubic hair development by age 11. These factors accounted for around one third of the variance in stage of pubertal development, which suggests other factors are likely to have influenced pubertal onset. These factors may be genetic, or environmental influences.

Social status and father figure at age 7 and age 11 were not significantly associated with pubertal development. However, there could be many other factors of the family environment, and other lifestyle and economic variables that impact overall circumstances, which were not measured for these girls, which could account for more of the variance in the mode. Moreover, in 1958 fewer children grew up without their biological fathers compared to the current UK population. More families had two married parents who were both the

biological parents of the child. Fewer parents cohabited or divorced, and the family unit was more consistent across the population than we see today.

Birth weight was not associated with pubertal stage at age 11, despite showing a significant association with age at menarche. This may indicate either periods of positive energy balance in later childhood, or perhaps a greater influence of weight status in later childhood than birth weight on pubertal onset compared with age at menarche. Moreover, this could reflect a degree of environmental tracking beyond the foetal period, which is considered a significant driver of growth trajectories (Barker et al., 1986, Hales and Barker, 2001). Critical periods of growth during childhood may contribute to pubertal trajectory by altering the growth set points of the individual relative to environmental quality, as is evident in migrant populations where girls move to environments with lower energetic and immune stress (Nunez de la Mora and Bentley, 2008).

Marshall and Tanner (1969) stated that there was a mean interval of 2.3 years between age at thelarche and age at menarche. From these data it was not possible to calculate the interval, however this dataset does show that the between-group difference for age at menarche based on breast stage at age 11 decreases with higher breast stage, which suggests that girls who mature earlier may reach menarche quicker.

The British Cohort Study 1970 (BCS70)

Tables 5.10 summarises anthropometric and measures for the cohort, and table 5.11 shows mean age at menarche as well as the proportion of girls beginning puberty by age 10 (in 1980).

Mean and median age at menarche for the girls in this cohort, who were born in 1970, was 12.55(SE.02), and 13.00 respectively. Birth weight was positively correlated with age at menarche (r=.04, p<.01). However, both weight at 10, and weight gain between 42 months and age 10 were negatively correlated with age at menarche (r=-.318, p<.001). No associations were found between age at menarche and weight in subsamples of girls at 22 months or 42 months respectively. Among 782 girls height at age 10 is significantly positively correlated with age at menarche (r=.178, p=<.001).

An independent-samples t-test found that girls who reached menarche before age 13 had greater weight gain between age 42 months and 10 years compared with girls who reached menarche at 13 or later (t(341.794)= 5.096, p<.001). Girls who reached menarche earlier were also heavier (t(2582.119)=13.666, p<.001) and taller at age 10 (t(2731.876)= 13.210, p<.001).

Table 5.10. Cohort anthropometric descriptive statistics BCS70

Age	**Height (cm)** **Mean(S.E)/Median(Range)**	**n=**	**Weight (kg)** **Mean(S.E)/Median(Range)**	**n=**	**% Reached menarche (n)**
Birth			3211.90(6.10)/3232.00(5131.00) **(g)**		
22 months	82.45 (.05)/83.00(63.00)	1083	11.56 (.05)/11.57(12.42)	1097	
42 months	92.75(.62)/96.50(116.70)	1073	13.90(.13)/14.51(30.00)	1073	
10	138.38(.09)/138.40(46.20)	5753	32.76(.08)/31.80(28.00)	5633	
13					79.4 (2259)
14					94.6 (3049)

Table 5.11 Cohort menarcheal descriptive statisticsBCS70

Evidence of puberty age 10	**N= (%)**	**Weight (kg)** **Mean(S.E)/Median**
YES	1481 (26.4)	36.12 (.15)/35.40
NO	4122 (73.6)	31.54(.08)/30.80
		Mean(S.E)/Median(Range)
Age at menarche	3222	12.55(.02)/13.00(5.00)

Figure 5.3 shows the distribution of initial signs of pubertal development across those girls who had begun puberty by age 10. Eighty-eight percent of girls entered puberty by the thelarche pathway, 9% via pubarche and the remaining 3% entered puberty with menarche or other as the initial sign.

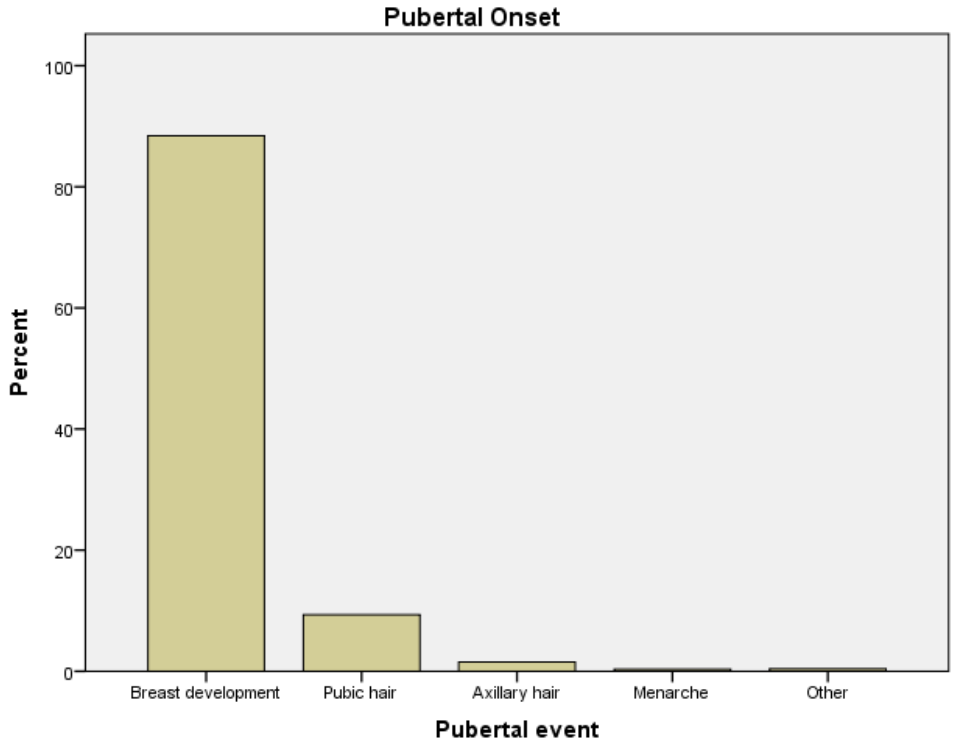

Figure 5.3.
Distribution of pubertal onset by initial pubertal event

Independent-samples t-tests found that girls who show evidence of pubertal development at age 10 had a significantly higher mean weight (M=36.12, SE=.15) than those who did not show any evidence of pubertal development at age 10 (M=31.54, SE=.08), t(2309.850)=-26.57, p<.001). Girls were also taller at age 10 (t(5718)= -24.100, p<.001), and heavier in early childhood at age 42 months (t(849)= -2.088, p<.05), and subsequently had greater mean weight gain between age 42 months and 10 years (t(807)--8.849, p<.001).

One-way ANOVA found no significant difference in age at menarche by ethnicity, father figure listed at age 5, or father figure listed at age 10. Ninety-one percent of girls age 5 lived with their natural father, and 85% of girls aged 10 lived with their natural father. Ninety-seven percent of the sample listed by ethnicity was white British.

A multiple stepwise linear regression found that weight at age 10 and weight gain from 42 months (age 3.5 years) to age 10 were significant predictors of age at menarche. Adjusted R^2=.11 (see table 5.12). Binary logistic regression found that height and weight age 10 were significant predictors of the likelihood of pubertal onset by age 10. R^2=.138, (Cox & Snell), .201 (Nagelkerke). Model $X^2(5)$ =116.128, p<.001 (see table 5.13).

Table 5.12 Stepwise multiple linear regression predicting age at menarche

Variable	**Estimate (B and SE)**
Intercept	14.586, .356***
Weight age 10 (kg)	-.043, .016**
Weight gain 3.5-9 years (kg)	-.032, .015*

Adjusted R^2=.11 *p<,05, **p<.01, ***p<.001.

Table 5.13. Binary logistic regression predicting evidence of puberty age 10

Variable	**Estimate (B and SE)**
Intercept	-11.682, 2.152***
Weight age 10 (kg)	.115, .020***
Height gain 10 years (cm)	.060, .018**

Note: R^2=.138 , (Cox & Snell), .201 (Nagelkerke). Model $X^2(5)$=116.128, p<.001. **p<.01, *** p<.001.

Discussion

Age at menarche is influenced by weight status at birth, in late childhood, and weight gain from early to late childhood. Heavier weight status at all of these stages is significantly associated with earlier age at menarche. Although girls who experience earlier age at menarche are heavier than peers and see greater gains in weight from early to late childhood, there is a positive correlation between height at age 10 and age at menarche; this relationship is likely the result of the additional growing years, and therefore delay, in epiphyseal fusion of girls who mature later. Indeed, girls who reach menarche before 13 years are taller at age 10, but of course girls who reach menarche later will gain that extra height over their early-maturing peers before they reach the milestone of menarche. The data are, however, right censored since some girls will not have reached menarche by age 16. Therefore, the true mean and median age at menarche is likely to be slightly later than is indicated by these results.

Just as early age at menarche is associated with higher weight status in early and late childhood, pubertal onset is similarly significantly associated with these factors. However, birth weight has no significant effect on the likelihood of girls showing signs of pubertal development at age 10. These results indicate that while very early life factors may determine age at menarche, age at pubertal onset could be more sensitive to the post-natal environment and particularly to energetic status and increases in weight across childhood.

When data were entered into a linear regression weight at age 10 and weight gain during mid-childhood to age 10 were the only significant predictors of age at menarche. This suggests that heavier girls are more likely to reach menarche sooner, and may also be evidence that adjustments in growth and maturation trajectory occur during childhood in response to positive energy balance, and may affect age at menarche. Similarly, a binary logistic regression found that only height and weight at age 10 were significant predictors of evidence of puberty at age 10. This may be indicative of a faster growth trajectory overall for girls who

mature earlier. This would also support evidence that girls who mature earlier are, on average, taller than their peers (He and Karlberg, 2001).

Exact age at pubertal onset was not measured in this cohort. Although there was a significant difference in mean weight in early developers, only around one quarter of girls had any indication of pubertal maturation by age 10. This might mask any effects on pubertal pathway of those girls who did not begin puberty by age 10. Additionally, since no pubertal scale was used to measure pubertal onset it is not known whether those girls who had begun puberty by age 10 were in the initial stage (e.g. B2 or PH2), or whether some of those (probably very few) were in more advanced stages of maturation. It also means we have no measure of *how long* it takes for girls to reach menarche after pubertal onset.

Onset of pubertal development was carried out by clinical examination, which should reduce bias from either overestimation or underestimation of maturation from girls when they were aged 10. However, there is no indication that breasts were palpated. In overweight subjects there is a tendency to overestimate breast development where fat tissue may be mistaken for the breast bud (Lee et al., 2006). However, fewer girls were overweight in 1980 - when pubertal onset was recorded in this cohort - compared with a contemporary sedentary population often in long periods of excessive positive energy balance.

Father absence and stepfather presence is shown to accelerate female pubertal maturation, since it reflects unpredictability in both levels of stress and parental investment (Draper and Harpending, 1982; Ellis and Garber, 2000). There is no evidence in this cohort to support such a hypothesis. This might either reflect a sample bias in the number of girls in the study living with both natural parents, but is more likely to reflect the lower rates of divorce and separation in 1970 Britain compared with the contemporary British population.

The strengths of these analyses are both the size of the cohort and the spread of the cohort from birth all across the UK, and large numbers of girls returning data across childhood for analyses across the data sweeps.

The Avon Longitudinal Study of Parents and Children (ALSPAC)

Table 5.14 and 5.15 give details of the cohort descriptive statistics (Christensen et al., 2010a; 2010b). Median age at menarche was 12.87. However, median age at menarche was latest for girls in the pubarche pathway (13.13), earliest for girls who entered puberty via the thelarche pathway (12.78), and intermediate for girls developing synchronously (12.84) (Christensen et al., 2010a; 2010b).

Girls in the thelarche pathway spent 3.7 years in Tanner breast stages 2-3, which is longer than other girls. They spend 1.5 years in Tanner pubic hair stages 2-3. Girls in the pubarche pathway spent a shorter time in breast stages 2-3 (2.4 years), and spent on average 3.3 years in pubic hair stages 2-3. Girls in the synchronous pathway spent 2.7 years in breast stages 2-3 and 2.2 years in pubic hair stages 2-3 (Christensen et al., 2010a; 2010b).

Table 5.14. Cohort pubertal onset descriptive statistics (ALSPAC)(Christensen et al., 2010a; 2010b).

Initiation pathway	**(%)**	**Median age at menarche (95% CI)**	**Median age at pubarche (95% CI)**	**Median age at thelarche (95% CI)**	**n=**
Thelarche	42.1	12.78 (12.7-12.9)		9.43 (9.4-9.5)	1482
Pubarche	11.6	13.13 (13.0-13.3)	9.44 (9.28-9.59)		408
Synchronous	46.3	12.84 (12.8-12.9)			1631
Total	100	12.87 (10.8-12.9)	11.00 (10.9-11.0)	10.20 (10.1-10.2)	3938

Table 5.15 Cohort descriptive statistics (ALSPAC) (Christensen et al., 2010a; 2010b)

Variable	**%**
Normal weight age 8	74.7
Overweight age 8	12.4
Obese age 8	10.4
Menarche by 14	62.7

Median age at pubertal onset was very young for both pubarche and thelarche pathway girls (9.4 years), compared with girls who developed synchronously (10.7 years). Thelarche pathway and pubarche pathway girls showed signs of their respective other secondary sexual characteristic relatively later than the sample median. Pubarche girls showed signs of thelarche at 11.3 years (sample median 10.2), and thelarche girls showed signs of pubarche at 11.6 years. As such, girls who enter puberty via the synchronous pathway spend the shortest period of time in premenarcheal pubertal development (2.3 years), followed by girls in the thelarche pathway (3.5 years), and girls who enter puberty via pubarche spend longest in premenarcheal pubertal development (3.9 years) (Christensen et al., 2010a; 2010b).

Being overweight or obese at age 8 was most associated with pubertal initiation via the thelarche pathway. Girls who were overweight or obese age 8 were more likely to begin puberty asynchronously than synchronously (Christensen et al., 2010a; 2010b).

Discussion

As girls have become fatter over time it is thought that there is a concomitant exaggeration of breast development. As girls self-report development of secondary sexual characteristics it is possible that the estimate for thelarche in particular could be earlier than the true age. This cohort is more likely than the others to see a greater degree of fatness among girls due to changes in diet, attitudes to food and snacking, and lower energy output among children, compared with the other datasets. In this case, girls were not clinically assessed for Tanner stage so there is room for speculation that girls were under- or over-estimating their pubertal stage. More significantly, a young girl who might be overweight and therefore have excess fat tissue on the chest area is unlikely to be able to distinguish that fat growth from glandular breast tissue. Therefore, girls might be more likely to positively identify the onset of breast development where this may in fact be lacking. This might explain some of the association between overweight, obesity, and thelarche. Girls were more likely to enter the

thelarche pathway if they were overweight. The thelarche pathway was also associated with an earlier age at menarche than pubarche or synchronous development.

Age at menarche was later in girls who entered puberty through the pubarche pathway, and became successively earlier via the synchronous pathway and thelarche pathway respectively. Additionally, median entry into the thelarche pathway was associated with the earliest signs of pubertal onset among the cohort. Therefore, the most overweight girls began puberty earliest, were more likely to begin pubertal development via the thelarche pathway, and reached menarche at a younger age than their lighter weight peers, although girls in the pubarche pathway spent longest in pubertal development before reaching menarche.

Age at pubarche for girls in the pubarche pathway was also comparable to thelarche in the thelarche pathway. It seems that asynchronous pubertal development is associated with earlier pubertal onset overall when compared with girls who develop relatively synchronously.

It is possible that while overweight and obesity in childhood is associated with an earlier pubertal onset via asynchronous pubertal development, the later age at menarche evident for girls entering puberty via the pubarche pathway could have an independent explanation. Early pubarche is often associated with catch-up growth. So, girls who are born lighter and who see significant catch-up growth in mid childhood are more likely to enter puberty via pubarche than girls born appropriate for gestational age (Neville and Walker, 2005). If this were the case it could be that growth in mid childhood rather than birth weight that has a greater influence on age at pubertal onset, but that birth weight lends a significant contribution to setting the trajectory for overall maturation, and therefore has a great influence on age at menarche than it may have on other aspects of maturation.

Additionally, weight and weight gain at different points in childhood may have differing effects on the HPO and nervous systems, which differentially mediate breast and pubic hair development (Christensen et al., 2010a; 2010b).

The strengths of this cohort are the large size, longitudinal design, repeated measurements of pubertal maturation in the adolescent years, and the geographic location, which makes increases the likelihood of successful follow-up.

Evidence for secular trends in age at pubertal onset and age at menarche from 1948-2005:

Results

Tables 5.16-5.19 (overleaf) show mean comparative data from the 4 datasets included in these analyses.

Results from the 4 datasets show evidence for a continued secular trend for younger age at menarche from 1948- 2005. Median age at menarche fell from 13.17 in the Harpenden cohorts to 13.00 in both the BCS58 and the BCS70 cohorts, to 12.87 in the ALSPAC cohort. That is a drop of 0.3 years over that period. Additionally, mean age at menarche showed a steady decline from 13.13 in the Harpenden cohort, to 12.72 in the BCS58, and finally to 12.55 in the BCS1970. These data highlights the drop in age at menarche of 0.17 years between the two British cohort studies, which is masked by the interval data collection when presented as a median.

In addition to the evidence for a continued downward secular trend in age at menarche there is also evidence for a downward trend in age at pubertal onset. Median age at pubarche fell from 11.61 in the Harpenden cohort to 11.00 in the

ALSPAC cohort, which is a drop of 0.61 years from 1948-2005. Over that same period age at thelarche has fallen exactly 1 year from 11.19 in the Harpenden cohort to 10.19 in the ALSPAC cohort. From these analyses the interval from B2 to menarche was 2 years for the Harpenden dataset (unable to confirm if the cases in this dataset directly match those measured in Marshall and Tanner, 1969, where the interval is stated as 2.3 years), and 2.7 years in the ALSPAC cohort.

Table 5.16. Comparative cohort mean height measures..

Height (cm)

	Harpenden	**BCS58**	**BCS70**	**ALSPAC**
42 months			92.75	
7		121.92		
9	132.49			
10	138.24		138.38	
11	142.95	144.73		
12	149.10			
13				
14				
15				
16	160.21	160.88		

*median

Table 5.17. Comparative cohort mean weight measures..

Age	**Weight (kg)**			
	Harpenden	**BCS58**	**BCS70**	**ALSPAC**
Birth **(g)**		3225.00	3211.90	
42 months			13.90	
7		23.66		
9	28.45			
10	31.77		32.76	
11	35.43	37.19		
12	40.24			
16	45.70			
BMI age 10 (kg/m^2)	16.62		17.10	
BMI age 11 (kg/m^2)	17.35	17.75		

*median

Table 5.18. Comparative cohort mean pubertal milestones..

	Harpenden	**BCS58**	**BCS70**	**ALSPAC**
Age at thelarche (years)	11.15, 11.19*			10.19*
Age at pubarche (years)	11.48, 11.61*			11.00*
Age at menarche (years)	13.13, 13.17*	12.72, 13.00*	12.55, 13.00*	12.87*
Menarche by age 13 (%)	82	75	79	
Menarche by age 14 (%)	95	95	95	

*median

Table 5.29 Comparative cohort evidence of pubertal onset.

	Harpenden	BCS58	BCS70	ALSPAC
Evidence of puberty age 8 (%)				12^, 5*
Evidence of puberty age 9 (%)				34^, 18*
Evidence of puberty age 10 (%)			26	58^, 40*
Evidence of puberty age 11 (%)		84		86^, 71*
Evidence of puberty age 16 (%)		97		

^thelarche, *pubarche

There is evidence that a significant proportion of the downward trend in age at pubertal onset has taken place between 1980 and 2005 (see table 3.5.1). The BCS70 cohort data show that in 1980 26% of girls showed signs of pubertal development when they were aged 10. By 2001/2 40% of girls had reached pubarche by age 10 and 58% of girls had reached thelarche by age 10. The figures for thelarche alone demonstrate that the proportion of girls beginning puberty by age 10 more than doubled from 1980-2001/2. The true figure will be even higher when those girls who developed initially by the pubarche pathway are included with the proportion of girls developing by thelarche and synchronous pubertal development. The figures from age 9 in the ALSPAC cohort demonstrate that a higher proportion of girls (34%) had evidence of thelarche by age 9 compared with the proportion of girls who showed any sign of pubertal develop by age 10 in 1980 in the BCS70 cohort.

In the Harpenden, BCS58 and BCS70 cohorts the same proportion of girls (95%) have entered puberty by the time they are 14 years of age. Therefore, the same proportions of girls in all 3 cohorts (5%) are late developers compared to the cohort means.

Discussion

These data support the predictions for hypotheses 1 and 2; both age at menarche and age at pubertal onset have shown a steady decline from 1948-2005. Age at menarche has fallen by 0.3 years, age at pubarche has fallen by 0.61 years and age at thelarche has shown the greatest decline of one full year from 1948-2005.

In all but one cohort (Harpenden) earlier age at menarche was predicted by increased weight status just preceding pubertal onset (age 11 in the BCS58, age 10 in the BCS70 and age 8 in the ALSPAC cohort). In the Harpenden cohort height at age 11 was the only significant predictor of age at menarche. This may be the result of the more restricted diet that girls in a Children's home would have had access to when compared with the general population. It is more likely that fewer girls would be much fatter than their peers if they were all eating the same diet; although this cannot account for girls who either refused food or ate less of their food compared to other girls their age. However, for all cohorts, girls who reached menarche before age 13 were either heavier preceding menarche or had greater weight gain in childhood. Moreover, girls in the BCS58 cohort had a higher mean BMI than girls in the Harpenden cohort at age 11; and girls in the BCS1970 cohort had a higher mean BMI than girls in the Harpenden cohort at age 10, which is evidence of the trend for increasing fatness in girls as the result of changing diet and lifestyle in the latter part of the 20th century and into this century.

Earlier age at pubertal onset is predicted by increased height and weight preceding puberty in the Harpenden, BCS58, and BCS70 cohorts. The significant drop in age at thelarche from 1948-2005 supports the evidence presented by Christensen et al (2010a; 2010b) that the interval between age at B2 and age at menarche is increasing. Age at menarche did, however, also fall over the same period, but it fell by only 0.30 years. When earlier age thelarche is considered relative to that change the interval between B2 and menarche has increased by 0.70 years from 1948-2005.

As these results also show (see table 3.5.1) the proportion of girls who reached thelarche by age 10 in 2001/2 has more than doubled since 1980, and a higher proportion of girls who reached thelarche by age 9 in 2001/2 is higher than those reaching thelarche by age 10 in 1980. Given that the earliest mean age at thelarche in the ALSPAC cohort (9.43), recorded for girls who entered puberty via the thelarche pathway, was predicted by overweight at age 8, this suggests that increased weight status is a strong predictor of both earlier pubertal onset, and particularly a trend for earlier age at thelarche from 1980-2001/2.

Although there were no associations between social class, adverse home conditions (stressful home environment) or the presence or absence of a father or stepfather figure, with earlier age at pubertal onset or earlier age at menarche in these analyses, these effects may have been masked by the study designs employed. Measures of household income may have predicted pubertal outcomes better than measures like social class as the labour market modernised and class became less of a universal measure over the period of study in these analyses. Moreover, had these analyses included data on father figure absence of presence in the ALSPAC cohort it may have been a predictor of pubertal outcomes since divorce rates in England and Wales peaked in 1993 (ONS, 2011), and although divorce declined throughout the 1990s, rates were still significantly higher than they had been in previous decades (ibid). This may have been reflected in the ALSPAC data since the cohort were born in 1991/1992, when divorce rates were just about to reach their peak.

The proportions of girls who had reached menarche by age 14 in the Harpenden, BCS58 and BCS70 cohorts were the same (95%). The remaining 5% of girls may therefore represent the expected number of girls in a sample to experience any one of a variety of disorders that is associated with pubertal delay, whether related to genetic conditions like Turner's syndrome (Rosenfield et al., 2006), or as the result of heavy exercise pubertal delay, common to gymnasts and ballet dancers (Baxter-Jones and Maffulli, 2002).

Although it is evident that the trends for earlier age at pubertal onset and age at menarche are predicted by concomitant increases in weight status among girls, these factors cannot account for all of the variance pubertal development. In addition to psychosocial factors and disorders of puberty associated with puberty timing, there is, of course, a genetic element to the prediction of pubertal milestones (Gajdos et al., 2010). Mother-daughter effects were not measured here, but are likely to have an effect. Indeed, data on mother's age at menarche is a predictor of age at menarche in girls in the ALSPAC cohort (Christensen et al., 2010a; 2010b).

These non-growth-related factors may well contribute to predictions of age at puberty, but their effect is unlikely to explain all of the variance that is unexplained by the models presented here. Indeed, many of the relationships between overweight and obesity, and female pubertal development highlighted in the previous Chapter – e.g. body shape and composition, fat patterning, and dietary content – were not analysed here because the data were not available.

Early age at menarche is associated with earlier onset of ovulatory menstrual cycles, and higher serum FSH even before menarche (Vihko and Apter, 1984). Longer exposure to high levels of steroid hormones is a known risk factor for breast cancer in adulthood (Jasienska and Thune, 2001). Moreover, early age at thelarche is also associated with early follicle activity and earlier ovulation (Crofton et al., 2005). Since early age at thelarche appears to have extended the interval between B2 and menarche then those girls with early thelarche (who should expect earlier age at menarche) have more opportunities for steroid hormone exposure than later maturing girls. These negative implications for health outcomes associated with increased weight status, higher exposure to potential endocrine disrupting chemicals, and early pubertal maturation (particularly early thelarche) deserve significant attention.

Conclusion

Analyses of longitudinal cohort data from 1948-2005 found evidence of a continued downward secular trend in median age at menarche of 0.30 years from 13.17 to 12.87. Over the same period, age at pubarche fell by 0.61 years, and age at thelarche fell by one year from 11.19 to 10.19. As a result of the greater decline in age at thelarche compared with age at menarche, the interval between Tanner breast stage 2 and age at menarche fell from 2.00 years to 2.70 years. More than half of the decrease in age at thelarche took place between 1980 and 2001/2. Although higher weight status is associated with earlier pubertal onset and earlier age at menarche it does not predict all of the variance in pubertal timing. The downward trends for age at menarche and age at pubertal onset (specifically thelarche) may be exacerbated by exposure to endocrine disrupting chemicals, which could put early maturing girls at increased risk of negative health outcomes.

Chapter Six: plasticity of female pubertal development in response to multiple environmental pressures

Early age at pubertal onset: the relationship between fat mass and EDC exposure

The analyses in Chapter Five found that the proportion of girls who reached thelarche by age 10 in 2001/2 has more than doubled since 1980, and a higher proportion of girls who reached thelarche by age 9 in 2001/2 is higher than those reaching thelarche by age 10 in 1980. Given that the earliest mean age at thelarche in the ALSPAC cohort (9.43), recorded for girls who entered puberty via the thelarche pathway, was predicted by overweight at age 8, this suggests that increased weight status is a strong predictor of both earlier pubertal onset, and particularly a trend for earlier age at thelarche from 1980-2001/2.

The results presented in Chapter Five suggest that while birth weight seems to interact with age at menarche - which could indicate a heritable or programmed growth trajectory in response to pre-natal cues - weight during early and later childhood is more associated with age at pubertal onset.

The significant drop in age at thelarche from 1948-2005 supports the evidence presented by Christensen et al (2010a; 2010b) that the interval between age at breast stage 2 (B2) and age at menarche is increasing. This extension of the pre-menarcheal period mirrors findings from the USA whereby girls who were overweight were more likely to begin puberty earlier than peers, and were more likely to begin puberty via the thelarche pathway compared with peers (Biro et al., 2003). However, what is unclear in the UK population is how this effect may be mediated by ethnicity. Schubert et al. (2005) found that non-white girls in the USA were more likely to have more breast development at a higher BMI than normal weight peers, whereas the ALSPAC population studied by Christensen et

al (2010a; 2010b) were almost all white British. However, despite homogeneity of ethnicity in the UK dataset higher weight status at age eight is associated with earlier age at thelarche.

Earlier pubertal onset has been associated with dietary changes over the last 30 years in the UK and USA, since long-term positive energy balance is associated with a greater proportion of energy available to growth and reproductive onset at an earlier age (e.g. Ebling, 2005). Diets have changed significantly during this period with a greater reliance on high-energy snack and convenience foods and a decreasing amount of fruits, vegetables and lean protein. But what is particularly striking about these findings from the UK datasets is the very fast acceleration of age at thelarche over just 20 years in the UK. More than half of the total decrease in age at thelarche in the UK over the last sixty years took place during that 20-year period.

During the period 1980-2000/1 dietary habits changed enormously. The introduction of ready meals and microwave meals, often high in salt and sugar, made convenience part of eating for the first time. In that same period more mothers were returning to work, and with limited time on their hands more and more families moved away from traditional family-based homemade meals, and more towards pre-made pre-packaged food. In schools there was also a huge amount of change that affected children's diets. Margaret Thatcher's tendering of school meals contracts in the UK, whereby schools were forced to accept the lowest bids for the contract, meant that the foods children were eating were no longer traditional cooking made from scratch, but processed foods high in additives since this was cheaper to produce.

Perhaps the most significant part of the changing diet and reliance on convenience foods is the use of compounds in their packaging that we now recognise as endocrine disrupting chemicals (EDCs). The possible effects of EDCs on pubertal onset may well account for some of the variance in age at pubertal onset not explained by weight status alone. As discussed in Chapter Three, there

is a plethora of data that suggests EDCs have the potential to interfere with endogenous hormones, particularly oestrogen (e.g. Colborn et al., 1996; Ouyang et al, 2005; Soto and Sonnenschein, 1983; 1984). The actions of EDCs on endogenous hormone levels present an interesting candidate mechanism for the acceleration in age at pubertal onset over the last 20 years.

Exposure to endocrine disruptors represents a significant aspect of lifestyle that has not been measured in this thesis, but has altered exponentially over the period of 1948-2005 (Dold, 1996; Sharara et al. 1998; Schoeters et al., 2007; Diamanti-Kandarakis, 2009). While not exhaustive, there is some evidence of EDC exposure and accelerated thelarche, whereby women in Puerto Rico exposed to phthalates experienced earlier thelarche (Colon et al., 2000). More broadly, EDCs have been linked to earlier puberty (Dickerson and Gore, 2007; Golub et al., 2008). As such, the possible role of endocrine disruptors on pubertal development, and specifically thelarche, should be explored further.

Although weight status at age 8 seems to predict falling age at thelarche this relationship may be exacerbated by endocrine disruptors, which are highly lipophilic and more likely to be found in higher concentrations in fatter individuals compared with leaner individuals who have had the same exposures (Colborn et al., 1996). I propose that *a relationship between EDC exposure and high relative fat mass* is associated with an early age at thelarche. Since EDC exposure was not controlled for in the analysis of the UK data, earlier thelarche could indicate the increasing prevalence of EDCs as well as overweight, but a relationship between the two factors may be a better explanation for the sharp acceleration in age at thelarche between 1980 and 2001.

A relationship between EDC exposure and high relative fat mass that has the potential to influence age at thelarche is based on two notions: 1) In the 20 year period where we see the sharpest acceleration in thelarche we began regularly heating plastics and using food packaging that is vulnerable to chemical breakdown; and 2) EDCs are highly lipophilic, which means a greater amount of

EDCs could be sequestered in the adipose tissue of a fatter individual relative to normal weight peers.

It has been around 20 years since EDCs were shown to leach from plastic materials upon heating in an autoclave (Krishnan et al., 1993). More recent research has shown that almost all plastic food containers (even BPA-free or microwave safe) release oestrogenic compounds upon heating (Yang et al., 2011), particularly phthalates (Bang et al., 2012). Other risks of leaching have been associated with plastic water bottles (Wagner and Oehlmann, 2009) – particularly when left in a warm environment like a car on a sunny day – and most controversially from babies' bottles when they are heated to sterilise, which can enormously boost the EDC burden of an infant (Aschberger et al., 2010).

Many households in the UK now use microwaves regularly, if not daily. Often, food is heated in plastic containers or takeaway cartons, which may leach oestrogenic compounds into the foods they contain. Other risks may be associated with other plastic or coated food containers like cartons, plastic milk bottles, Tetrapak containers etc. Many of these contain a barrier coating between the package and the food item. The lacquer coating that lines some tins has been shown to have oestrogenic effects (Brotons et al., 1995), and the same may apply to these numerous types of food cartons and packages.

The lipophilic nature of EDCs means there is a potential for concentrations to be proportionally higher in fatter individuals. Girls who are fatter could therefore be sequestering more EDCs. Some EDCs are obesogenic (Grun and Blumberg, 2007; 2009) meaning they may support or encourage obesity by interfering with fat storage mechanisms, again increasing the potential storage capacity for EDCs (ibid).

The point of peak height, or peak height velocity (PHV) may be a possible time at which exposure to EDCs and their relative concentrations in fat stores may interact with mechanisms of pubertal onset. Some EDCs are excreted via hepatic routes (Alstrup and Slorach, 1991), but some compounds are still capable of remaining stable in adipose tissue. However, during a growth spurt some of the energy held within adipose stores is utilised. At this point there is the potential for a cocktail of sequestered EDCs to flood the body and interact with other systems, including the endocrine system. A pool of oestrogenic compounds that floods the body during a growth spurt may have the potential to accelerate the mechanisms involved in pubertal onset, or thelarche. For fatter girls this would create a unique risk from both higher EDC loads overall, and the possible interaction of obesogens that may have contributed to overall fat mass.

The possible mechanisms for the interaction of EDCs with mechanisms of pubertal onset demands further attention. The body of literature detailing all of the possible and known effects of xenoestrogens and other EDCs is growing rapidly, but little is known about the actions of EDCs released from fat stores.

Early age at pubertal onset: an adaptive response

Early age at puberty is associated with a number of negative health and behaviour outcomes. The potential accelerating effect of an interaction between exposure to endocrine disruptors and increased weight status in girls on puberty timing could increase the risk of such negative outcomes further. Indeed, early menarche is associated with many risk-taking behaviours such as smoking, drinking alcohol, early onset of sexual activity, and increased incidences of risky sexual encounters (Downing and Bellis, 2009).

An important consideration of the acceleration of pubertal onset, and in particular the lengthening of the pre-menarcheal pubertal period, is the health implications. Earlier age at menarche is associated specifically with higher rates of reproductive cancers (Jasienska and Thune, 2001), but that doesn't mean the

same negative health outcomes are predicted by earlier age at pubertal onset. Detecting a relationship between the timing of pubertal onset and adult health outcomes would rely on determining whether earlier pubertal onset influences the speed with which girls begin regular ovulatory cycles after menarche, and whether a longer period developing before menarche accelerates the maturation of the hypothalamic-pituitary axis (HPO).

One example of a population who similarly have a lengthened period of pre-menarcheal maturation was presented in Chapter Two. The Kikuyu of Kenya live in circumstances far removed from the UK populations detailed here, yet they display some striking similarities to a model of puberty we consider novel, or indeed pathology. As discussed in Chapter Two, it might be more helpful to consider recent change in the process of puberty as sitting on a continuum of normal, adaptive plasticity, rather than medicalizing change as pathology. Our models of "normal" puberty and "normal" ovarian function – clinically speaking – are typically based on Western populations who are not only better nourished, wealthier and freer from disease than many living populations, and those of our evolutionary past, but represent the minority of the real variation in developmental and reproductive capacity. Perhaps placing our understanding of normal in its true context is the most reliable way of understanding the limits of phenotypic plasticity. This would also provide a framework with which to model and theorise novel contexts that may be utilising existing, or dormant plasticity.

Phenotypic plasticity in female pubertal development likely evolved as the result of uncertain environments. As humans exploited new ecologies they would have had to adapt to new selection pressures on reproduction. The extent of phenotypic plasticity will no doubt be tested further still as urbanisation provides new, energy-saving niches, and humans continue to produce materials that have the potential to disrupt reproductive strategi

Conclusion

The variation in pubertal development evident across all populations, coupled with our extensive knowledge of the process of puberty in developed nations, highlights the necessity to carefully consider whether trends in pubertal development, and changes in pubertal strategy should be considered pathology. In response to earlier age at pubertal onset in some western populations, clinicians seem to be concerned with medicalizing puberty to fit within normative values or pubertal scales. However, developmental plasticity in female pubertal development is a demonstration of the inextricable link between genetic function and environmental context. Although early maturation is unusual in human history it is yet another example of a life history strategy that has adapted to new environmental selective pressures.

It is possible for some girls to mature incredibly young, and for some to delay maturation into early adulthood. Some girls will speed through puberty to mitigate risk, and others benefit from the extra growth time they gain before they are fully physiologically mature. Of most concern in all of these circumstances should be both recognising the energetic constraints –or lack thereof- in a given environment and understanding the relative benefits and possible risks both during pubertal growth, and on later health, associated with girls' pubertal development.

While earlier age at puberty may serve to benefit females in risky environments- whether due to food insecurity, stressful or violent home life, or high immune burden- in order to increase the time over which one can contribute to total fertility rate and therefore increase overall reproductive fitness; a similar pubertal strategy, within an overall reproductive strategy, can pose significant health risks to a well-nourished, healthy individual. The evolutionary history of an adaptive reproductive strategy appears to support a very wide range of

phenotypic plasticity that may not, as yet, be tested to its full capability, and is unlikely to have posed the same risks to health in pre-historical ecologies.

This thesis has answered hypothesis 1 and found that there was a continued secular trend for earlier age at menarche, which fell by 0.3 years between 1948-2005. This thesis also answered hypothesis 2 and found a significant decrease in age at pubertal onset of 1 year, which is associated with higher weight status preceding pubertal onset. This thesis could not answer hypothesis 3, but suggests a possible mechanism for the role of endocrine disrupting chemicals in accelerating pubertal onset.

This thesis has addressed both original aims to understand the changes in female pubertal development over the last sixty years, and to consider those changes as an evolved response.

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Appendix 1

Variables available for analyses from UK cohort datasets:

Variable	Harpenden	BCS58	BCS70	ALSPAC
Birthweight (oz)	✓	✓	✓	
Father social class		✓	✓	
Weight age 3			✓	
Weight age 6				
Weight age 7		✓		
Weight age 8				✓
Weight age 9	✓			
Weight age 10	✓		✓	
Weight age 11	✓	✓		
Weight age 12	✓			
Weight age 13	✓			
Weight age 14	✓			
Weight age 16	✓	✓	✓	
Height age 3			✓	
Height age 6				
Height age 7		✓		
Height age 8				✓
Height age 9	✓			
Height age 10	✓		✓	
Height age 11	✓	✓		

Height age 12	✓			
Height age 13	✓			
Height age 14	✓			
Height age 16	✓	✓	✓	
Evidence of puberty age 10			✓	
Evidence of puberty age 11		✓		
Evidence of puberty age 16		✓	✓	
Pubertal development age 13				
Age at thelarche	✓			✓
Age at pubarche	✓			✓
Age at menarche	✓	✓	✓	✓
Menarche by age 13	✓			
Menarche by age 14	✓			
Menarche by age 16		✓	✓	