UNIVERSITY OF SOUTHAMPTON

THE SHORT NORMAL CHILD: INFLUENCES ON THE GROWTH PATHWAY AND FINAL HEIGHT OUTCOME

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If only one fish could be found in the sea, people would probably have noticed how perfect it was.

THE CHRISTMAS MYSTERY,
JOSTEIN GAARDER

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF MEDICINE, HEALTH AND BIOLOGICAL SCIENCES
ALLERGY, INFORMATION AND REPAIR

Doctor of Philosophy

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By Jean Mulligan

Short stature is a common reason for a child to be referred for specialist opinion. Most will have no underlying pathology but dismissing a short child as normal may impose future suffering as the short adult is perceived to be psychosocially disadvantaged and to face greater health risks. Adult height, however, cannot be predicted from childhood height with any degree of certainty.

Growth begins at the moment of conception and ends with epiphyseal closure some two decades later. Height, however, is not accumulated at a fixed rate throughout the growing process but consists of four distinct phases: foetal, infancy, childhood and pubertal. The intensity and duration of each phase is subject to wide variation and poor growth in any one phase does not inevitably compromise final height. To a large extent, both stature and the tempo of growth are genetically determined but social and environmental factors can have a modifying effect. For some children, poor environmental conditions can cause growth to falter but equally an improvement in quality may result in catch-up growth.

The Wessex Growth Study is the first study to follow the growth of an unselected population of short normal children from school entry until final height together with controls of 'average' height. A great deal of background information was also collected for each child including parental heights, birth history, social & family background, and medical history. To determine which short normal children become short adults this thesis has compared the patterns of growth of short normal children with their average height controls and assessed the impact of genetic and environmental variables on the growth pathway and final height.

Before puberty, short children grew more slowly than those who are taller but the magnitude and duration of the pubertal spurt and the adolescent height gain were similar for short and control girls, and for short and control boys. The pubertal spurt of short normal boys, however, occurred, on average, some six months later than expected. Interestingly, although short normal girls had similar birth weights, skeletal delay and were just as likely as short normal boys to be considered short for family, the timing, magnitude and duration of their pubertal spurt were comparable with the control girls and with Tanner's standards.

The mean height centile of both groups improved suggesting a continuing secular trend in adult stature within the UK. Nevertheless, the increase in relative height was greater for the short children implying some degree of catch-up growth, especially for boys. Indeed, short normal girls were three times more likely than short normal boys to attain an adult height below the 0.4^{th} centile and below their genetic potential. Some short children have become taller adults than others but in relation to their peers, a substantial number have remained short and failed to reach their genetic potential. Growth is influenced by many factors, genetic, social, environmental and emotional, but few variables were found to be predictors of the adult height of short normal children and much of the variance remains unexplained.

This thesis demonstrates the individuality of the growth pathway and the difficulty in identifying those who will become short adults. Recognising which children might benefit from intervention requires a multi-professional team including the growth specialist, social worker and psychologist.

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ABBREVIATIONS

BMI	Body mass index
C	Control
CDGP	Constitutional delay of growth and puberty
FSH	Follicle stimulating hormone
FSS	Familial short stature
GH	Growth hormone
GnRH	Gonadotrophin releasing hormone
HSDS	Height standard deviation score
IUGR	Intrauterine growth retardation
LH	Luteinizing hormone
PAH	Predicted adult height
RUS	Radius, ulna short bones
SD	Standard deviation
SDS	Standard deviation score
SN	Short normal

FOREWORD

Heightened awareness of short stature and its causes has contributed to an increased referral rate from the community to specialist clinics. Indeed, routine height screening at school entry is recommended, as many experts believe that this provides a unique opportunity to examine the whole population and produce an acceptable yield of previously undiagnosed pathology [Hall 2000]. Such a programme, however, will undoubtedly identify an even larger number of short but otherwise healthy children raising concerns among parents. There is a widespread belief, mainly based on methodically flawed research, that the short adult is socially and psychologically disadvantaged. The introduction of synthetic growth hormone in 1985 seemed to provide a solution by offering clinicians an almost unlimited supply and giving them the option of treating all cases of short stature, even those with no pathological base. Before such treatment can be considered, however, two issues need to be resolved. First, is short stature per se a condition that warrants medical intervention? Second, do short normal children necessarily become short adults?

The Wessex Growth Study was established in 1986 to address these questions. As a prospective, community based study it aimed to overcome many of the methodological issues in previous research. A total population of short but otherwise healthy children were to be included providing a large, unbiased sample with no cases of self-referral. All would be selected from school entry height screening with each short child having a taller control of the same age and gender. The physical growth and psychological development of these children would be monitored in the community, without intervention, from school entry to final adult height in order:

1. to establish whether there is any link, at any age, between short ***normal*** stature and psychological or social functioning.
2. to observe the patterns of growth of short normal children and determine how many short normal children ultimately become short adults.

This thesis is concerned with the latter question. Adult stature is the culmination of foetal, infant, childhood and pubertal growth but within each phase, individuals vary in both the rate of maturation and intensity of growth. Although stature and the rate of maturation are largely

inherited characteristics, many social and environmental factors can have a modifying effect on both these factors. The aims of this thesis therefore are:

(i) to examine the patterns of growth and final height outcome of short normal children in a community setting and compare these to children of average height.

(ii) to assess the impact of biological and environmental parameters on final height outcome.

This thesis consists of seven chapters:

Chapter 1 describes the pattern of normal growth from birth until adult stature and reviews the factors that influence height attained and the rate of maturation.

Chapter 2 describes the recruitment procedure to the Wessex Growth Study and details the methods used to describe the growth pathway from recruitment at the age of 5 years until the attainment of adult stature.

Chapter 3 focuses on the pre-pubertal growth of the short and control children examining the role of genetic and environmental variables in the control of growth.

Chapter 4 is concerned with the adolescent years when differences in the tempo of growth are more clearly seen. The timing, magnitude and duration of the pubertal spurt of short and control boys and girls are compared and factors which influence the adolescent height gain are examined.

Chapter 5 examines the effect of pre-pubertal and pubertal growth on the adult height of short and control children to determine the extent, if any, of secular trend and catch-up growth. The influence of biological and environmental variables on final height is also examined.

Chapter 6 provides a summary of the findings of this thesis.

Chapter 7 is a validation study of the methods used in this thesis to describe the pattern of growth.

Chapter 1: NORMAL CHILDHOOD GROWTH

Hypothesis: *Although stature is largely genetically determined, environmental factors can have a modifying effect such that prepubertal height cannot confidently predict adult height but, by examining the genetic and environmental variables associated with childhood growth, it will be possible to identify the very short child destined to become the very short adult.*

1.1 The Short Normal Adult

The short adult is perceived to be disadvantaged [Underwood 1991]. It has been reported that short stature results in poor job prospects, social isolation, and low self-esteem [Macintyre 1988]. More recent reports have emphasised the greater health risks faced by short people who are more likely to die from heart disease and stroke [Parker et al 1998, Forsen et al 2000]. These findings have initiated a debate as to whether short stature, in the absence of disease, is a condition that warrants intervention [Kelnar et al 1999, Saenger 1998, Stabler and Underwood 1999, Haverkamp and Ranke 1999]. One possible treatment is the pharmacological manipulation of height with substances such as growth hormone [Taback et al 1999]. Where there is a hormonal deficiency, such treatments are appropriate and are likely to improve final height [Sandberg and MacGillivray 2000].

Most short children, however, have no obvious pathology to explain their short stature and are often termed 'short normal' [Hindmarsh and Brook 1987]. When such children appear in growth clinics, the clinician is faced with a dilemma. Both pharmacological and physiological tests diagnosing growth hormone deficiency are unreliable [Rosenfeld et al 1995, Butler 2001], and many syndromes, such as Silver-Russell and Noonan, rely on clinical acumen for their diagnosis. Moreover, dismissing a child as 'short normal' may impose future suffering as short stature is reported to be detrimental to both adult health [Silventoinen et al 1999, Wamala et al 1999] and psychological well-being [McDaid and Finkelstein 1994]. Consequently, many experts consider that growth disorders should be diagnosed using auxological criteria alone [Milner 1986, Hindmarsh and Brook 1988, Werther 1996].

The advent of synthetic growth hormone (GH) in 1985 seemed to provide a solution. Clinicians were then assured of an almost unlimited supply of growth hormone giving them

the option of treating all cases of short stature, even those with no pathological cause. The ethical and moral issues of treating short but otherwise healthy children are vast and are being strongly debated [Verweij and Kortmann 1997, Oberfield 1999, Voss 2000, Saenger 2000,]. However, to be effective, growth hormone treatment must begin in early childhood, well before the onset of puberty [Tanner 1975] and this poses yet another dilemma; while the clinician can be sure that the short prepubertal child with growth restricting pathology will become a short adult unless given the appropriate treatment, the outcome for the short normal child, whether treated or untreated, is uncertain [Preece 1988a, Hintz 1996, Wit et al 1996]. It is also apparent that much of the earlier work reporting the social and psychological disadvantage of short stature was methodologically flawed [Stratford et al 1999, Voss 2001]. Many of these studies were conducted with clinic referred samples without controls and often contained mixed diagnostic groups [Holmes et al 1985, Stabler et al 1994]. It is now evident that in some pathological conditions, such as Turner, Noonan and Silver-Russell syndromes, specific psychosocial problems are associated more with the condition than stature itself [Skuse et al 1994b, Lai et al 1994, van der Burgt et al 1999]. There is in fact little evidence that the short but otherwise healthy individual is in any way disadvantaged.

It was against this background that the Wessex Growth Study was established. This study is a community based, longitudinal study that has monitored the growth and psychological development of an unselected population of very short children since 1986. The aims were to assess the impact of their stature on their psychological development, and to establish whether short stature at any age presents a disadvantage. The children were recruited from two adjacent health districts as they entered primary school in 1985/1986 and all short children, who had no pathology to explain their short stature, were included. Over 14,000 children were measured and 142 short normal children were identified of whom 140 agreed to participate. Each of these children was age- and gender-matched with a child in the same school class whose height was between the 10^{th} and 90^{th} centiles. The recruitment procedure is described in Chapter 2.

Adult height, however, cannot be predicted from childhood height with any degree of certainty. Birth size reflects the interuterine environment rather than the foetal genotype and consequently the correlation coefficient between birth length and subsequent adult stature is only in the order of 0.3 [Tanner et al 1956]. During infancy, however, this rises sharply such that by the age of 3 years the correlation between childhood and adult heights is

approximately 0.8, where it remains until the start of puberty [Tanner et al 1956]. Even with a correlation as high as this, the difference in adult height of prepubertal children of similar height may be as much as 15cm with approximately 30% of the variability in adult height resulting from differences in the adolescent growth spurt [Tanner 1989]. Figure 1.1 shows the height and height velocity of two short normal girls in this study. Before puberty, both had almost identical heights and similar patterns of growth. Differences in the timing and magnitude of the adolescent spurt, however, resulted in one (***A***) becoming a very short adult with a height below the bottom centile line while the other (***B***) had a final height within the expected range. Interestingly, girl ***B*** had taller parents than girl ***A***, whose mother's height was 3 standard deviations below the mean.

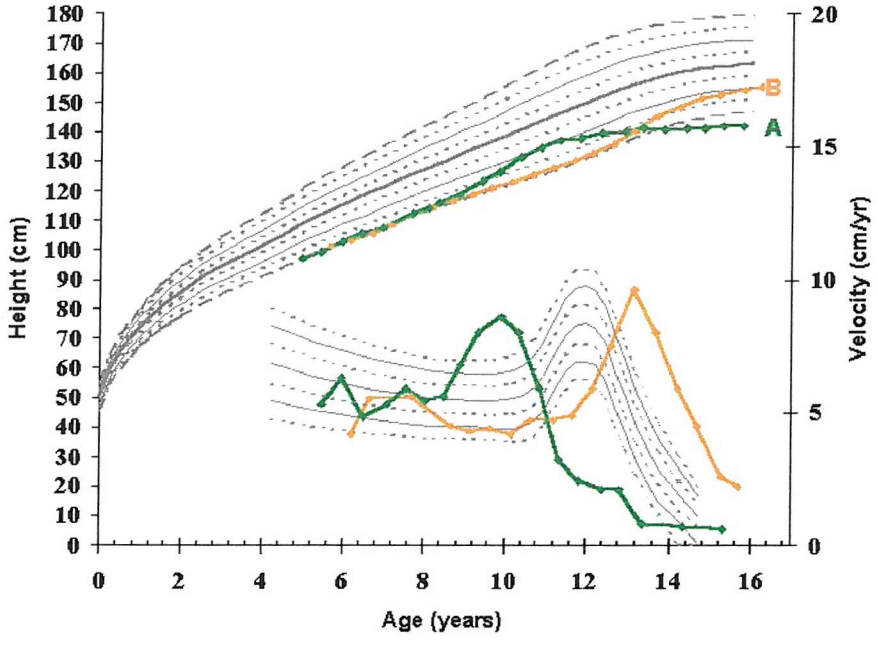


Figure 1.1 *Height and height velocity of 2 girls illustrating the effect on final height of the timing, magnitude and duration of puberty*

1.2 The Genetic Inheritance of Stature

Stature is largely an inherited characteristic as twin studies clearly demonstrate [Wilson 1986a, Hauspie et al 1994, Silventoinen et al 2000]. From the age of 1 year, the correlation of the heights between monozygotic twins, who are genetically identical, is reported to be as high as 0.94 while that of dizygotic twins lies somewhere between 0.5 and 0.8. The genetic control of stature is also evident from the variation in adult height of siblings compared with that of the general population. For most populations, the range in height of adult males is

approximately 25cm around the mean [Eveleth 1986] but only 16cm among brothers brought up together [Hauspie et al 1982].

Several biological variables, such as birth size and parental height, are also associated with short adult stature [Kuh and Wadsworth 1989, Karlberg and Luo 2000]. Whether these variables are purely genetic is far from certain. Birth weight, for example, is thought to be influenced more by environmental factors such as social class, mother's health, and alcohol and tobacco use, than genetic makeup [Cogswell and Yip 1995]. Parental height, too, may reflect an environmental component, especially for those who are short. The short adult is more likely to remain in low-paid, unskilled employment and be socially disadvantaged [Bielicki and Waliszko 1992, Power et al 2002].

Nevertheless, a strong family resemblance in height is apparent. Short parents ***do*** tend to have short children while tall parents have tall children. Indeed, the correlation between the heights of parents and their offspring is of the order of 0.5 [Tanner et al 1970, Kuh and Wadsworth 1989, Tambs et al 1992], and Preece (1996) has demonstrated the agreement between actual and theoretical correlation coefficients for adult stature and various family relations assuming a polygenic model of inheritance. The pathway to final height, however, is not prescriptive. As an illustration, figure 1.2 shows the growth of three boys from this study whose parents were of similar heights. The final adult heights of these boys were also very similar, but their childhood heights had at times been quite different.

1.3 The Growth Pathway

There are, in fact, four distinct growth phases that contribute towards adult stature: foetal growth, infancy, childhood, and puberty [Karlberg 1989]. During each phase, however, individuals vary in two important parameters – rate of maturation *and* intensity of growth. These differences are most apparent during the initial and final phases of growth. For example, the normal prenatal period is considered to last between 37 and 42 completed weeks from mother's last menstrual period with approximately 1 in 10 infants born outside these limits. Those born prematurely, before 37 weeks, tend to be lighter, but even for those born at term, there is considerable variation in birth size with healthy, newborn term infants weighing as little as 2500g or as much as 5000g. Differences in the rate of maturation and intensity of growth are also evident during the pubertal phase of growth, which is characterised by a sharp increase in height. This occurs earlier in girls than boys but, even

within the sexes, there is wide variation [Buckler 1990]. The height gain during puberty depends on the intensity and duration of the adolescent spurt and gains of between 20 to 40 cm and between 11 to 29cm have been reported for boys and girls, respectively [Buckler 1990]. There are also some children, especially boys, who seem to have a prolonged childhood period of growth with pubertal development delayed by more than two years [Albanese and Stanhope 1995]. The variability in the rate of maturation and in the intensity of growth during each phase results in the variability in adult height and the age at which this occurs.

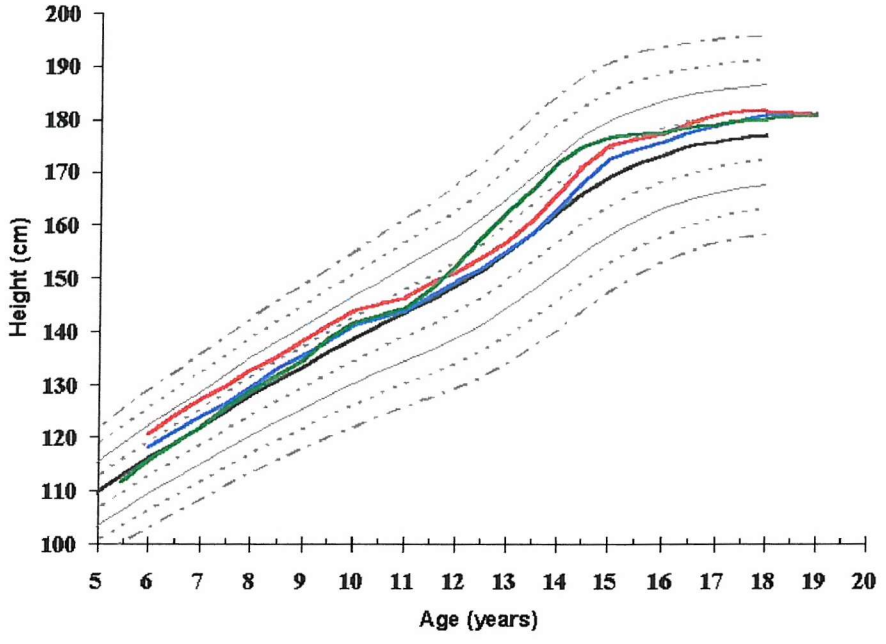


Figure 1.2 *The growth pathway of 3 boys from this study. Although adult heights were very similar, the growth pathways were quite different.*

Poor growth in any one phase of growth does not inevitably compromise final height. Foetal growth is largely dependent on mother's size and the intrauterine conditions [Cogswell and Yip 1995], but there is evidence to suggest that the effect of this prenatal environment does not necessarily persist. As might be expected, birth size and gestational age are positively correlated with those born prematurely tending to be shorter and lighter [Keen and Pearse 1988]. By the age of 1 year, however, this correlation has disappeared. Indeed, regardless of gestational age, there is a tendency for smaller babies to display rapid postnatal growth in both weight and length, especially during the first 6 months of life [Tanner 1994]. A good example of this is the case of monozygotic twins who share the same placenta. Falkner

(1966) found larger within-pair discrepancies in the birth weights of monozygotic twins, presumably as a result of an unequal supply of nutrients, than in dizygotic twins. After birth, however, the growth rate of the smaller identical twin generally exceeds that of the larger and by the age of one, much of the disparity has disappeared [Wilson 1986b]. This phenomenon, termed *catch-up* growth, is not restricted to the infancy phase of growth but can occur throughout childhood, even in the final adolescent phase of growth [Largo 1993].

Brush and Harrison (1990) have suggested that childhood growth consists of a genetic component and an environmental component. They have hypothesised that the genetic component of growth velocity is constant over time while the environmental component is variable but limited by genetic factors, and that it is this environmental component that causes growth to slow or allows catch-up growth to occur. Several authors have in fact demonstrated that episodes of acute illness, chronic conditions, and starvation can cause growth faltering, but once the growth restriction is addressed, a phase of rapid growth is commonly reported until the pre-illness growth curve is reached [Prader et al 1963, Tanner 1981b, Largo 1993].

1.4 Environmental Influences on Stature

The environmental influences on body height are most clearly seen in developing countries where there is a marked difference in the living conditions of those from advantaged homes and those from poor families where malnutrition and disease is common [Eveleth and Tanner 1990]. Bogin et al (1992) have reported a mean difference of 7.7cm in the adult height of two groups of Guatemalan children living in very different conditions. Those living in more favourable conditions were taller and heavier at all ages. Even in industrialized nations, such as the UK, where childhood health is generally good and nutrition adequate, adult height has been shown to be socially patterned [Macintyre 1988]. Indeed, a study of over 3000 men and women in the UK found that less than 30% of the variance in adult height was explained by parental heights [Kuh and Wadsworth 1989]. Clearly, there remain other influences that are of importance.

Prenatal growth

Foetal growth is now considered to be crucial to future health and development [Barker et al 2001]. Birth weight is commonly used as an indication of foetal growth. Low birth weight is often the result of adverse social circumstances [Goldstein 1981, Kogan 1995] and several

sources suggest that the consequence of low birth weight on subsequent growth is not fully reversible. For example, a number of studies have shown that although infants whose birth weights were less than the 10th centile do show some catch-up growth, many become short adults and attain a height below genetic target [Karlsberg and Luo 2000, Zucchini et al 2001]. Indeed, Falkner (1966) clearly demonstrated the long-term effect of intrauterine malnutrition in the case of one set of monozygotic twin boys born at term with extremely disparate birth weights of 1460g and 2806g, respectively. Although some degree of catch-up occurred during infancy, the lighter twin was over 5cm shorter at the age of 16 years. Even when birth weights are more evenly distributed, the lighter twin tends to become the shorter adult [Ijzerman et al 2001, Loos et al 2002]. However, it may be that birth size itself is not the cause of short adult size but the ongoing circumstances responsible for low birth weight in the first place.

Family environment

Many studies have now confirmed that somatic growth depends not only on genetic potential but also on the environment in which a child grows up [Goldstein 1971, Rona et al 1978, Rona 1981, Mascie-Taylor 1991, Tanner 1992]. Children of manual workers are consistently found to be shorter than those of non-manual workers in the early school years. Furthermore, Kuh and Wadsworth (1989) studied the effect of childhood environment on adult height. After adjustment for parental heights and birth weight, they found that low social class, overcrowding, large family size and high birth order increased the risk of adult short stature. These same factors were also found to be a significant influence on the adult height of participants in the 1958 National Child Development Study [Power 1991].

Psychological stress

Short childhood stature has also been associated with psychological stress [Skuse 1989a, Mascie-Taylor 1991]. In dysfunctional families, infants suffering from emotional, physical or sexual abuse are more likely to display growth failure, even when food intake is adequate [Skuse 1989b, Stanhope et al 1994]. Few studies have examined the long-term effects of family stress but there is some evidence to suggest that these persist throughout childhood and into adult life. A community study investigating 'family factors' associated with child development found that the 'quality of care' given to a child during the first three years of life was the most important factor affecting not only height but also behaviour and cognitive function during the primary school years [Neligan and Prudham 1976]. One Swedish

population study also reported that short adult stature was more common among those who had grown up in an atmosphere of conflict, even if this did not result in family break-up [Peck and Lundberg 1995].

Growth starts from the moment of conception and height achieved reflects both pre- and postnatal influences. It would appear that poverty and stress impact at multiple levels affecting not only nutritional levels but also lifestyle patterns that are not conducive to optimal growth. Short stature in adulthood may well be an indication of adverse psychosocial conditions in childhood.

1.5 Normal Childhood Growth

The earliest and most published longitudinal record of growth was made between 1759 and 1777 by Count Montbeillard. His friend Buffon, a scientist, had persuaded him to measure his son from birth to maturity. Many anthropologists and auxologists have since revisited this data, first published in 1777, in their examination of the process of human growth. Tanner (1981a) plotted the data to show both the curve of growth and growth rate (figure 1.3). These illustrate clearly the three phases of growth, as described by Karlberg (1989), of infancy, childhood and puberty.

Growth in infancy (figure 1.4a) is rapid but the rate of increase rapidly decelerates in the first few years of life. By the age of three years, the rate of deceleration in growth velocity has levelled off to a slower but steadier pace, which continues during the childhood phase of growth (figure 1.4b) reaching its nadir in late childhood. The transition between childhood and adolescence is marked by a sharp increase in growth rate, which rises to a peak and then immediately begins to decrease again (figure 1.4c), disappearing when epiphyseal fusion has been complete. This adolescent spurt is a constant phenomenon that occurs in all normal children although there is a marked difference between the sexes in its timing and magnitude. For girls, the spurt begins earlier and is smaller in magnitude. To a large extent, the difference in height between adult men and women is the result of this difference in pubertal growth.

Pubertal growth contributes a significant amount to final height. On average, for both boys and girls, some 16% of adult height is due to the adolescent growth spurt, but the range is

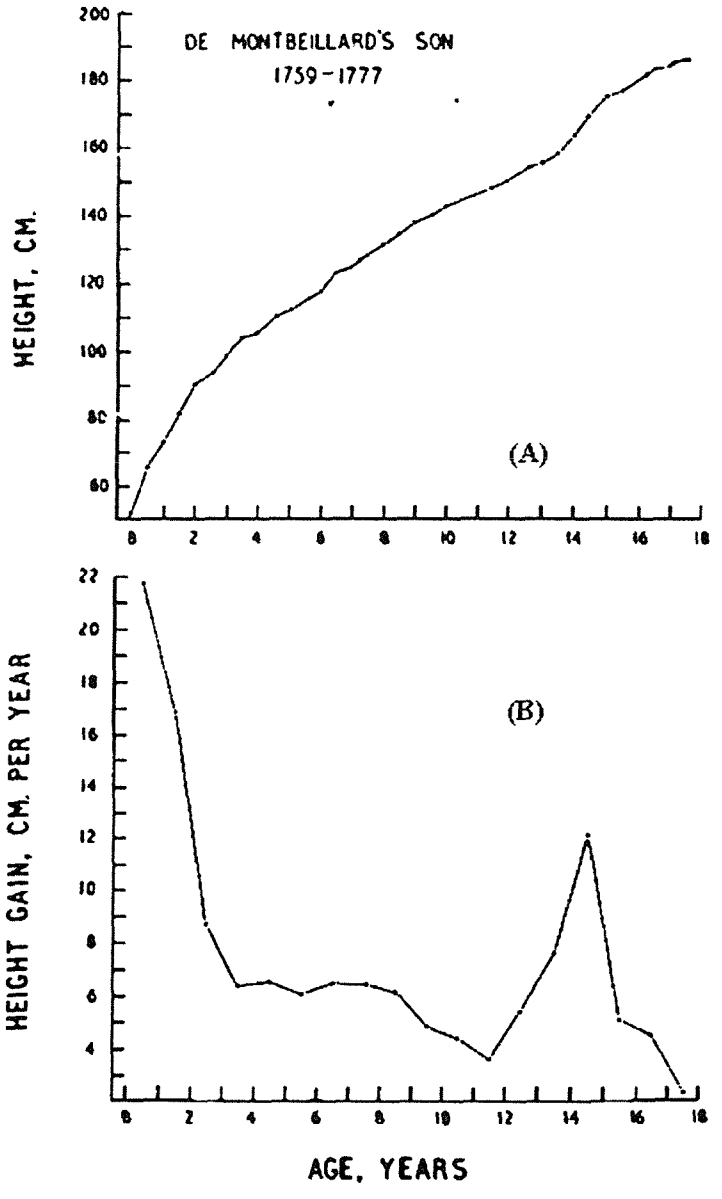


Figure 1.3 *Growth in (A) height and (B) height velocity of de Montbeillard's son from birth to 18 years*

considerable [Tanner et al 1976]. It is believed that the imprecision of adult height prediction methods are caused by the variability of pubertal growth [Preece 1988b, Hintz 2001]. The correlation between height immediately before puberty and adult height is 0.8 [Tanner 1956]. This means that a prepubertal child of average height is likely to have an adult height somewhere between the10th and 90th centile while the short prepubertal child may well become an adult of extreme short stature or one with normal stature (figure 1.1). Consequently, accurate prediction of pubertal growth would be of value to the clinician in the assessment and treatment of short stature.

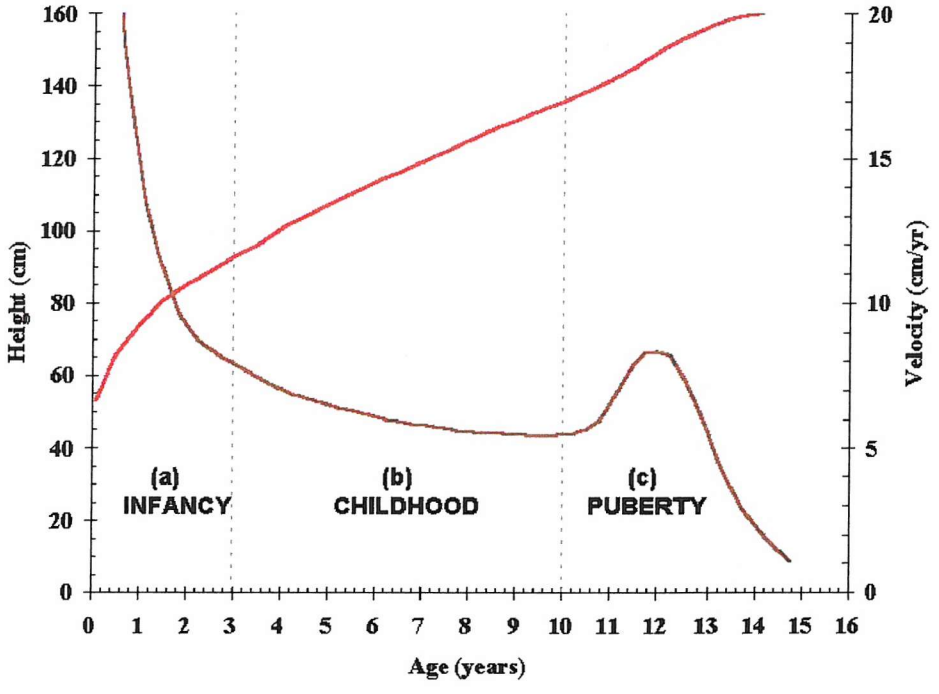


Figure 1.4 *Height — and height velocity — for a typical 'healthy' girl from birth to maturity showing the three phases of postnatal growth (a) infancy, (b) childhood and (c) puberty*

The adolescent growth spurt is clearly visible from an individual's height velocity curve, allowing both the magnitude of the peak height velocity and the age at which it occurs to be determined. Longitudinal growth studies have shown that the absolute value of peak height velocity (PHV) and the age at which it occurs varies from one child to another [Tanner et al 1976, Buckler 1990]. Current British standards of pubertal growth were constructed from the data of 49 boys and 41 girls who had been measured every three months throughout adolescence [Tanner and Whitehouse 1976]. From this data, the mean (SEM) age at PHV for boys was found to be 14.06 (0.14) years with a standard deviation of 0.92 years and, for girls,

12.14 (0.14) years with a standard deviation of 0.88 years. The pubertal spurt therefore occurs some two years earlier in girls and, for both boys and girls, the difference between early and late developers is approximately four years. Girls also displayed a somewhat less intense peak than boys, the mean value calculated over a whole year being 8.4cm/yr and ranging from 6 to 10.5cm/yr while the corresponding value for boys was 9.5cm/yr with a range of from 7 to 12 cm/yr. Gender differences in the intensity and timing of the peak are well documented and consistent among all populations [Marshall and Tanner 1968]. As illustrated in figure 1.5, modest correlations have been found between the magnitude of PHV and the age of its occurrence such that there is a tendency for those with early adolescent growth spurts to have greater PHV [Tanner et al 1976].

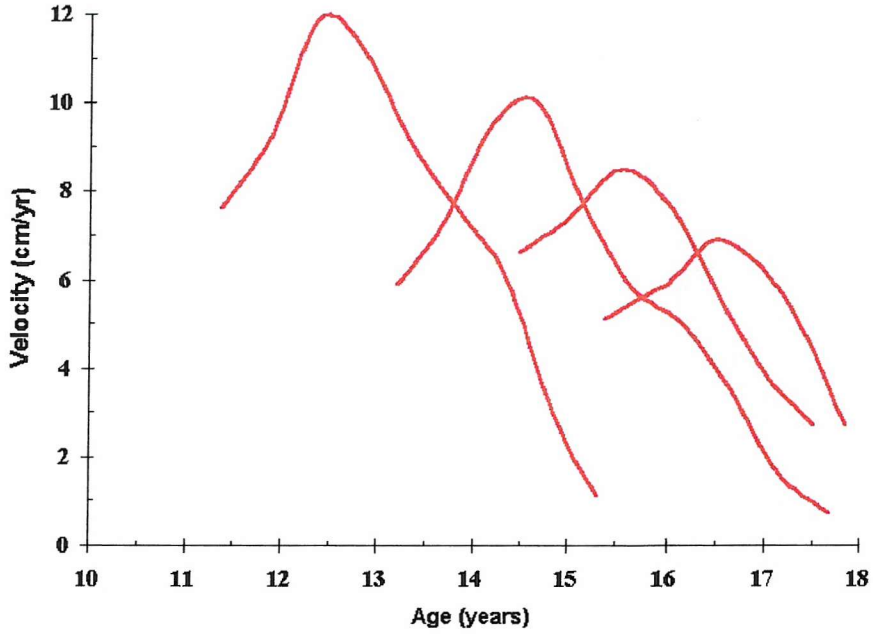


Figure 1.5 *Pubertal spurts of four boys in this study illustrating the correlation between age and magnitude of peak height velocity*

The time at which the adolescent spurt begins varies from child to child and so the mean curve, obtained by treating the values cross-sectionally, characterises the average pubertal spurt very poorly. Shuttleworth (1937) illustrated the difference between cross-sectional averaging and averaging after adjusting for the age of PHV. Figure 1.6a shows a series of individual curves plotted against chronological age with the average curve shown as a dotted line. By comparison, the average curve obtained after aligning individual curves so that their points of peak velocity coincide is sharper and more intense (figure 1.6b).

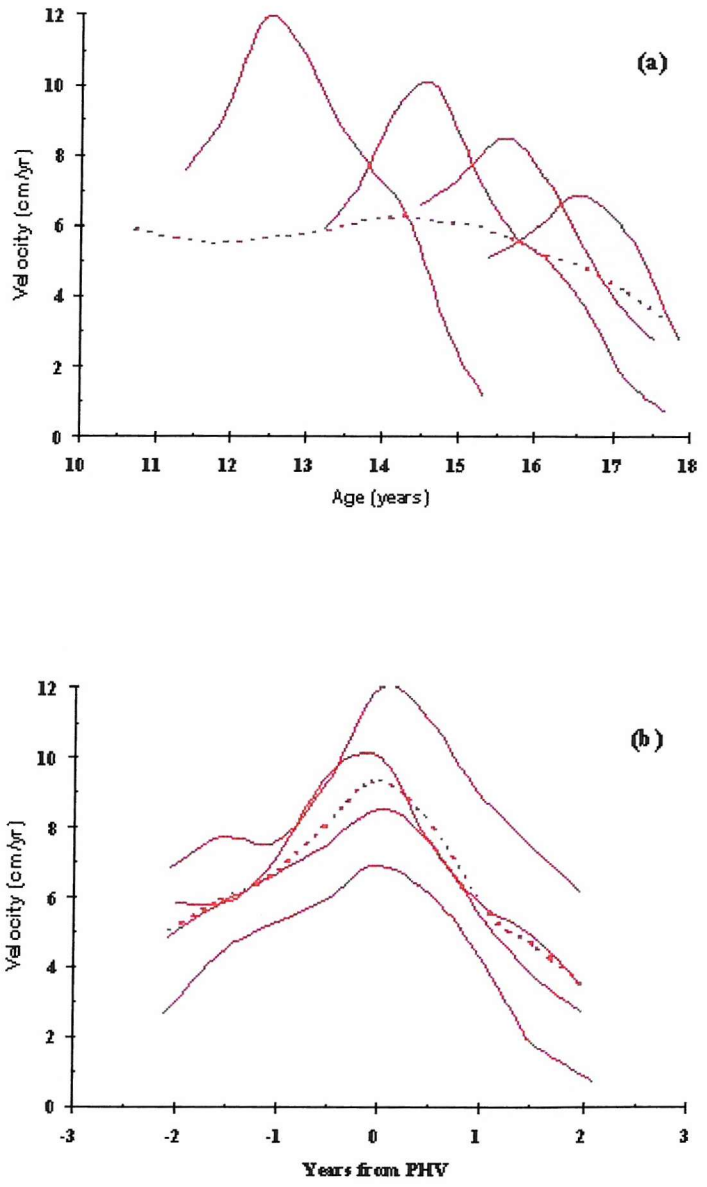


Figure 1.6 *(a) the individual height velocity curves of 4 boys from this study plotted against chronological age with the average curve shown as a dotted line. (b) the same curves plotted after aligning individual curves so that their points of peak velocity coincide. The average curve obtained is sharper and more intense*

Pubertal development is not an isolated event but involves large changes to both body size and body shape. The growth spurt in height is linked to growth in pubic hair and breast and genitalia development through each pubertal staging as described by Tanner. Stage 1 represents the appearance before any sign of pubertal development while stage 5 represents full adult appearance. However, the sequence of events in relation to the growth spurt, and the onset and rate of maturation of each process varies greatly across adolescents such that pubertal stages cannot be reliably used as a proxy for pubertal growth [Marshal and Tanner 1968, 1969, 1970]. The exception to this, at least for girls, is menarche. The onset of menstruation is a well-marked and dramatic event of puberty that invariably occurs after peak height velocity and is often used as a marker of the rate of maturation. Even in older women, recall of the age at menarche has been found to be reliable and so can be collected retrospectively [Bean et at 1979].

Growth is under the control of the endocrine system [Grumbach 1980, Wilkin 1997]. The endocrine glands secrete and discharge them into the blood stream in response to hormonal messages originating from the hypothalamus. Hormones necessary for normal growth from birth to adulthood include thyroxin from the thyroid gland, androgens from the adrenal gland, testosterone from the testis, oestrogens from the ovary, insulin from the pancreas as well as growth hormone and gonadotrophins from the pituitary gland. No hormone is more important than any other. All are required to act both independently and in concert to achieve the adult state. Growth hormone (GH) is the principal hormone influencing somatic growth. It is necessary at all ages, even playing a part in adult physiology [Lamberts et al 1997, Carrel and Allen 2000]. The effect of GH is to stimulate the production of liver-derived insulin-like growth factor-I (IGF-I), which in turn stimulates longitudinal bone growth. Recent reports, however, have demonstrated that GH also has a direct effect on tissue growth [Ohlsson et al 2000]. During puberty, GH secretion increases causing the adolescent growth spurt and reaches its highest level with the occurrence of PHV [Martha et al 1989, Rose et al 1991]. Thereafter GH reduces to the young adult value and then gradually diminishes with age. The major stimulus to this increase in GH secretion appears to be a rise in sex hormones in particular oestrogen in girls and testosterone in boys. The differences in the timing and intensity of the pubertal spurt are likely to be the result of the interaction of growth hormone and sex steroids [Brook and Hindmarsh 1992, Mauras et al 1996].

The onset of puberty is a critical stage in a sequence of complex maturational changes that begin before birth. For both sexes, the trigger is the production of gonadotrophin releasing hormone (GnRH) from the hypothalamus, which in turn stimulates the pituitary gland to release follicle stimulating hormone (FSH) and luteinizing hormone (LH). These hormones activate the ovaries in girls to produce oestrogen and progesterone and the testes in boys to secrete testosterone. The hypothalamus-pituitary-gonodal axis, however, develops early in the foetal period and, in the first half of gestation, high levels of GnRH, LH and FSH play an essential part in gender differentiation [Grumbach 1980]. As pregnancy progresses, a restraining system develops inhibiting GnRH release and producing a negative feedback to sex steroids. Although a transient rise in GnRH occurs shortly after birth, this central restraint operates during childhood until its removal or attenuation signals the onset of puberty [Delemarre-van de Waal 2002].

The precise mechanism by which this restraint is removed remains unclear, but recent research has focused on the relationship between fat metabolism and the reproductive system [Ong et al 1999, Clayton and Trueman 2000, Faloia et al 2000]. Leptin is secreted in adipose tissue and there is increasing evidence of its involvement in the control of puberty. Case studies of several families with mutations in either leptin or the leptin receptor have observed that affected members have no pubertal development, even as young adults [Clement et al 1998, Strobel et al 1998]. During the normal growth and development of both sexes, leptin increases gradually over the prepubertal years suggesting a permissive role in the progression into puberty [Clayton et al 1997]. Compared with boys, girls have a higher percentage of body fat as well as higher levels of leptin even before puberty, which may explain to some extent the gender difference in the timing of puberty [Ellis and Nicolson 1997].

Adipose tissue is also an important source of oestrogen [Cooper et al 1996] and the importance of oestrogen in female pubertal development is well established [Juul 2001]. At puberty, rising oestrogen levels in girls coincide with the increase in growth hormone secretion. Recent reports, however, have emphasised the biphasic nature of oestrogen and its role in the regulation of the growth spurt for boys as well as girls: low concentrations stimulate the growth of both males and females, but continued exposure is responsible for epiphyseal maturation which eventually results in the cessation of growth [Klein et al 1996, Culter 1997, Ritzen et al 2000, Delemarre-van de Waal 2001]. Klein et al (1994) reported significantly higher oestrogen levels in prepubertal girls compared with prepubertal boys and

suggested that this greater secretion might drive the more rapid skeletal maturation and earlier puberty in girls. Alternatively, the combined action and interaction of oestrogen and testosterone in boys may produce not only the gender differences in the timing but also the magnitude of the pubertal spurt. Although oestrogen may initiate puberty in boys as well as girls, testosterone release in boys acts to increase growth velocity by stimulating growth either directly or indirectly through a restraining effect on bone maturation [Loesch et al 1995]. Even within the sexes, however, there is wide variation in timing, intensity and duration of the pubertal spurt.

1.6 The Tempo of Growth

As early as 1891, Bowditch observed that the distribution of heights became skewed during the pubertal years with the upper centiles of height moving further away in the early pubertal years. He concluded that the pubertal spurt occurred earlier in taller children than short. Boas, however, was the first to realise that some individuals are further along the road to maturity than others throughout their childhood. Indeed, the phrase *'tempo of growth'* and the concept of developmental age are attributed to him. He observed that children with a slow tempo of growth were shorter throughout childhood than those with a rapid tempo of growth but that slow growers tended to have a delayed pubertal spurt and continued to grow for longer.
The differences in the rate of maturation become apparent at puberty, but they are present throughout childhood. In order to assess how far each individual child has progressed towards maturity, some measure of physiological age is required. Chronological age and height are unreliable. At any age, a child's height depends on their genetic potential and their rate of maturation. In normal, healthy children these variables are considered to be totally unrelated [Tanner 1986b]. Tallness may be the result of a rapid tempo of growth in a child destined to become an adult of average stature or, alternatively, may denote tall adult stature in a child with an average tempo of growth. Although the range in pubertal development is wide [Marshall and Tanner 1969, 1970], the age at entry to the various stages of puberty is a valid measure as all children pass through the same stages. This measure, however, is only meaningful during the ages of normal adolescent development. In prepubertal children, dental maturity has proved useful in assessing developmental delay [Krekmanova et al 1997]. While each of these methods has its own particular use, they are only weakly correlated and cannot provide a continuum [Tanner 1989]. One measure that is applicable throughout the whole period of growth is *skeletal maturity* or *bone age*.

Bone Age

Bock (1986) analysed the data for individuals followed from birth to final height. He compared the height, rate of growth and skeletal development of four women: the tallest, the earliest maturing, the shortest and the latest maturing. Both the tallest and the earliest maturing women were equally tall throughout infancy and childhood and their growth rates were also similar, but the early maturer had stopped growing by the age of thirteen while the tallest woman continued to grow until the age of 18 years. Similarly the late maturer was short during childhood but her slow rate of development resulted in a prolonged growth period and attainment of average stature. The difference in the patterns of growth of these four women was accounted for by rate of skeletal maturation as estimated from hand and wrist radiographs. From early childhood, the skeletal development of the early maturer was found to be advanced over her chronological age while that of the late maturer was delayed. Chronological age is not therefore a good measure of developmental age but bone age, as measured by a hand and wrist x-ray appears to be a measure of the skeletal maturity and the tempo of growth throughout childhood.

Interestingly, the adult height of these four women was appropriate for parents leading Bock to conclude that a major genetic component was responsible in the determination of both final height and the rate of maturation.

1.7 Genetic influence on the Rate of Maturation

As discussed earlier, stature has a strong genetic component. Population studies indicate that the rate of growth is also affected by genetic makeup. Bogin (1988) plotted the mean height velocity curves for three populations: a sample of British boys, a sample of boys from West Africa, and a sample of Australian Aborigine boys. He found marked differences in both the timing and intensity of the pubertal spurts. Compared with British and Aborigine boys, adolescent growth occurred later and was more prolonged for West African boys and, although the timing and duration of puberty was similar for British and Aborigine boys, the intensity of the spurt was greater for the Aborigine boys. Worldwide population differences in the age of menarche have also been observed [Eveleth and Tanner 1990]. Furthermore, in a large cross-sectional study of European, Afro-Caribbean and Indo-Pakistani girls living in London significant differences in menarcheal age were reported among these three ethnic groups [Ulijaszek et al 1991].

The influence of genes on the rate of maturation is supported by twin studies, which show greater concordance among identical twins in markers of maturation rate, such as dental age, skeletal age, and age at peak height velocity. In a study of dental maturation, Pelsmaekers et al (1997) showed that dental age was more similar for twins who were monozygotic than for those who were dizygotic. Wilson (1986b) analysed the longitudinal growth of twins and demonstrated that the heights of monozygotic twins became increasingly convergent in the adolescent years indicating that most aspects of the pubertal growth spurt were highly hereditary, a finding confirmed by others [Hauspie et al 1994, Beunen et al 2000]. Moreover, Loesch et al (1995), who investigated the relation between skeletal maturation and pubertal growth in identical and non-identical twins, concluded that growth in stature and skeletal maturation relies on highly integrated genetic processes.

Differences and similarities in the rate of growth, however, may equally be attributed to differences and similarities in the environment as well as the gene pool or may even be the result of an interaction between the two. Different populations tend to have different environments while twins share much of their environment as well as their genes [Philips et al 2001]. The heredity of the rate of maturation is in fact difficult to determine. Although measures of maturity, such as dental maturity, skeletal maturity, pubertal staging and age at peak height velocity are considered to be reliable indicators of the rate of maturation [Tanner 1989, Sinclair 1989], family data of this nature with sufficient statistical power to be definitive is difficult to ascertain either prospectively or retrospectively. For girls, menarche is one marker of the rate of maturation that can be used with a degree of confidence. Even in older women, recall of the age at menarche has been found to be reliable and so can be collected retrospectively [Bean et al 1979]. Twin studies again show that identical twin girls reach menarche within two to three months of each other [Fischbein 1977]. The difference is greater for non-identical twin girls but there are still highly significant sister-sister and mother-daughter correlations of around 0.4. Nevertheless, while these studies demonstrate the strong genetic component in the rate of maturation, they also suggest that a large amount of the variability in maturation rate is caused by external events. Moreover, parents and their children tend to share the same environment as well as the same genes and the high parent-child and sibling-sibling correlation may well be the result of the combined effect of environment and genes.

1.8 Environmental Influences on the Rate of Maturation

Nutrition, illness and socio-economic status

Nutrition, illness and socio-economic status are often linked together in human populations. In developing countries where all these factors are operative, developmental delay is evident [Martorell et al 1994]. The adolescent growth spurt is delayed and adult height is reached at a later age. However, where malnutrition is severe and persistent, catch-up growth to full adult potential is unlikely in spite of this prolonged growth period [Satyanarayana et al 1989, Kanade et al 1999]. By contrast, children subjected to an episode of acute starvation, such as in wartime famine, recover more or less completely. The undernourished child simply slows down and waits for better times [Tanner 1989].

In third world countries, where living conditions are poor, poverty is invariably associated with protein-calorie undernutrition, which in turn gives rise to high rates of infectious diseases such as gastroenteritis that further aggravate the problem of undernutrition. In such circumstances, it is difficult to attribute the effect of each factor. In Western countries, however, such as the UK, were chronic infectious disease is rare and nutrition is adequate even among the very poor, environmental factors, such as nutrition, disease and socio-economic status, have also been found to influence the rate of maturation.

Nutrition

Adequate nutrition is clearly important for normal growth and development. Malnourishment due to chronic disease, such as cystic fibrosis, coeliac disease, and Crohn's disease, result in slow childhood growth and delayed pubertal development [Preece et al 1986, Pozo and Argente 2002]. On the other hand, the obese child is generally taller from early childhood but sexual development occurs earlier and the accompanying growth spurt is somewhat reduced [De Simone et al 1995]. Even in non-obese subjects, overnutrition in early childhood has been shown to influence both the timing and magnitude of the pubertal spurt [He and Karlberg 2001]. In a population study, these authors retrospectively examined the growth patterns of over 3000 children and found that those who gained the most weight between the ages of 2 and 8 years tended to have earlier spurts and reduced height gain in adolescence.

Indeed, it has been suggested that puberty is triggered by a rise in subcutaneous body fat [Vizmanos and Marti-Henneberg 2000]. As discussed earlier, body fat, particularly

subcutaneous fat, is correlated with leptin, which is now thought to be responsible for the onset and regulation of puberty. Interestingly, obesity in boys has been associated with both early ***and*** delayed pubertal development [Vignolo et al 1988, Kaplowitz 1998]. For both males and females, leptin levels rise around the age at puberty, perhaps as a result of a rise in subcutaneous body fat. As puberty progresses, leptin levels in girls continue to rise but decrease in boys once testosterone and gonadotropins levels increase [Blum et al 1997, Kaplowitz 1998]. Kaplowitz (1998) has hypothesised that the higher leptin levels in obese adolescent boys may inhibit the effectiveness of testosterone and delay pubertal progression after testicular enlargement has occurred.

Atopic disease

Systemic chronic conditions such as cystic fibrosis, coeliac disease and renal failure, undoubtedly delay pubertal development [Preece et al 1986, Pozo and Argente 2002]. Most of these conditions though are rare and the growth patterns of such children are not representative of the normal population. Atopy, however, is a variable condition that is increasingly being diagnosed and treated among the normal childhood population [Anderson et al 1994]. The increasing rate of atopic disease in children and the widespread use of steroid treatment have prompted investigation into the effect of both the disease and its treatment on growth [Russell 1994]. Short-term studies reported decreased growth velocity and concluded that atopic disease and/or its treatment are responsible for growth failure in childhood [Kristmundsdottir and David 1987, Doull et al 1995]. Long-term longitudinal studies, however, confirm that growth suppression occurs only during the prepubertal years and is caused by delayed pubertal development but, once the pubertal spurt is complete, adult height is unaffected [Martin et al 1981, Balfour-Lynn 1986, Patel et al 1997, Patel et al 1998]. It remains unclear whether delayed puberty is a result of the disease and its severity or the treatment [Hindmarsh et al 1993].

Social environment

Historically, longitudinal studies of growth have shown marked differences in the timing of puberty for both populations and individuals [Tanner 1981]. A major contributor in this area was Frank Boas who published a series of papers describing the variability in growth and rate of maturation between populations of people, especially migrants to the United States and their children. Even within the same ethnic group, however, within population differences occur. One of the earliest longitudinal studies, conducted between 1772 and 1794 on students at the Carlschule in Stuttgart, showed that the sons of nobility were taller than those of the

middle class during the growing years. This advancement in maturation, however, had little effect on final height as both groups achieved approximately the same adult height [Komlos et al 1992]. Since this early study, others have reported differences in the rate of maturation associated with social class as measured by father's occupation [Billewicz et al 1981, Hulanicka and Koltlarz 1983]. Those from poorer families tend to have later pubertal development.

As discussed earlier, many studies have confirmed that somatic growth depends not only on genetic potential but also on the environment that a child grows up in. At all ages, those from more deprived backgrounds are shorter than those from the most advantaged. It would appear, however, that much of the height discrepancy due to poor social circumstances is established before the age of five and does not alter significantly during the prepubertal phase of growth [Smith et al 1980]. A large cross-sectional analysis of skeletal maturation confirms this finding and suggests that the rate of maturation is also affected by poor living conditions [Cole and Cole 1992]. Bone age assessment of over 1500 radiographs showed that social deprivation, as measured by unemployment, overcrowding and single parent families, results in a slower tempo of growth well into the adolescent years and affected younger and older children to the same degree. Moreover, a link between family size and the age at menarche has consistently been reported with those girls from larger family groups tending to have later menarche [Tanner 1962, Roberts 1986, Ulijaszek et al 1991].

Psychological stress

There is also evidence that environmental stress influence the timing of puberty though the effect may be gender dependent. For girls, stressful life events, such as family conflict, perceived parental disapproval and reconstituted families are reported to hasten pubertal development [Weirson et al 1993, Graber et al 1995]. A longitudinal study of over 200 girls also found that skeletal maturity occurred at an earlier age for those living in dysfunctional families [Hulanicka et al 2001]. On the other hand, a stressful environment appears to delay the onset of puberty in boys. Investigating the impact of family stress on the pubertal development of adolescent boys, Malo and Tremblay (1997) found that the presence of an alcoholic parent or low social position were associated with pubertal delay. Belsky et al (1991) argue that pubertal maturation is an adaptive response with its roots in natural selection theory and for girls the most adaptive response is to reproduce early and often. For boys, the most adaptive response may be to remain childlike as suggested by Bogin (1994).

Prenatal Growth

Recent reports have suggested that the pathway of growth and onset of puberty may be linked to prenatal exposures. The evidence, however, is conflicting and it would appear that this too might be gender dependent. Bacallo et al (1996) examined the relation of birth weight, height at age 14 years and the maturation process in a sample of 260 (130 boys) school children. They found that those who were more sexually mature were, on average, heavier at birth and taller throughout childhood, but that the effect was greater for boys than for girls. On the other hand, earlier menarche and rapid pubertal progression in girls has been linked to low birth weight [Cooper et al 1996, Ibanez et al 2000]. An interaction between birth weight, gender and pubertal development was also noted by Persson et al (1999). In a longitudinal study investigating the prenatal influence on the onset of puberty, these authors examined the birth and growth records of over 1200 adolescents. Birth weight was again found to be positively correlated with height at pubertal onset. For the boys in the study, none of the prenatal risk factors studied seemed to influence the onset of puberty, but girls born small or short for gestational age experienced their growth spurt earlier. Several other studies, however, have shown that the effect of birth weight on the timing of puberty is modified by early childhood growth and that rapid postnatal growth is independently related to earlier pubertal maturation [Adair 2001, Silva et al 2002].

1.9 The Short Normal Child

Short stature is a common reason for a child to be referred to a paediatrician. Most, however, will have no underlying pathology to explain their short stature. One large population study investigating the growth of over 100,000 American children found growth-related pathology in less than 8% of children whose heights were less than the 3rd centile [Lindsay et al 1994]. Short normal stature, also interchangeably termed 'normal variant short stature' [Rudman et al 1980], 'constitutional short stature' [Horner et al 1978] and 'idiopathic short stature' [Price 1996], is often sub-divided into 'familial short stature' (FSS), where the child is appropriate for family size or 'non-familial short stature' if the child is shorter than genetic expectation [Ranke 1996]. Non-FSS is typically characterised by a delay in skeletal maturation and later catch-up growth is assumed.

Indeed, many short normal children, especially boys, are referred for specialist opinion during the normal adolescent years when a diagnosis of constitutional delay of growth and

puberty (CDGP) is likely [Albanese and Stanhope 1995]. Such children do have a delayed bone age and often attain a spontaneous increase in relative height after the completion of the pubertal spurt [Price 1996]. However, in most cases, little is known about their growth in infancy and early childhood. It may be that the height of these children had only transiently fallen across the centiles as growth slows during the final stage of childhood growth. On the other hand, the short child referred in early childhood is often dismissed once pathology has been ruled out, especially if bone age is delayed and predicted adult height is within the expected range. In contrast to the short normal adolescent with CDGP, the pre-pubescent child diagnosed as 'short normal' is unlikely to be seen again and very little is known of his/her future growth and final stature. Indeed, it may be these children who become the short normal adults.

Accurate prediction of adult height would be of value to the clinician in the assessment of these children and a number of methods are available. These have been reviewed by several authors [Preece 1988b, Bramswig et al 1990, Hintz 2001] who have concluded that adult height prediction is imprecise, varies with the method used and is inaccurate. One possible explanation for these findings may be that most methods have been developed from groups of children with heights within the expected range while height prediction is generally used for children with extreme stature, short and tall. Alternatively, as suggested by Hintz (2001), the underlying problem may be the considerable individual variation in the timing and tempo of puberty that significantly impacts on the validity when applied to individual children. Preece (1988b) investigated the source of errors in height prediction and concluded that improvement would not be possible unless a measure could be identified that would accurately predict the timing of the adolescent growth spurt from early childhood.

The Wessex Growth Study has monitored the growth of short normal children and their average height controls since they entered primary school at the age of 5 years until final height. As well as collecting height and weight data, a great deal of background information is also available for each child, which includes parental heights, birth history, social & family background, and medical history. The study provides a unique opportunity to compare the patterns of growth of a large, homogeneous group of short normal children and their average height controls, and to assess the impact of genetic and environmental variables on the growth pathway and final height outcome.

1.10 Defining Short Normal Stature

The children studied for this thesis were identified from routine growth screening at school entry. Growth screening, however, requires a definition of normal and abnormal stature that can be recognized by comparing the individual child to population standards. At the time of recruitment in 1986, the current UK growth standards were those of Tanner and Whitehouse [Tanner et al 1966a, 1966b]. In line with the recommendations of the day [Hall 1989], short stature was taken to be a height below the 3rd centile, the bottom line on these charts. There is, however, no universal agreement. For instance, the USA has chosen the 5th centile [Tanner and Davis 1985] while others prefer to use standard deviation or z scores [Sempe et al 1979]. Whatever, the chosen criterion, it should be remembered that it is merely an arbitrary cut-off point below which a certain proportion of the population will lie. For example, the 3rd centile implies that 3% of the normal population will have a height below this point provided that the standards chosen are appropriate for the population screened.

Since the beginning of the industrial revolution, children in the UK have been getting taller and maturing earlier [Rosenbaum 1988]. Tanner also noted this trend and, on introducing the 1965 growth standards for height and weight, recommended that growth standards should be revised every 10 or 15 years until this trend stopped [Tanner 1966a]. However, a large-scale nationwide survey in 1972 suggested that the standards were still applicable and that the trend towards increased height had diminished [Rona and Altman 1977]. Consequently, when the Wessex Growth Study was established in 1986, the 1965 growth standards of Tanner and Whitehouse were still considered to be appropriate for British children at that time. Subsequent studies and data from the Wessex Growth Study demonstrated that, for height at least, the secular trend towards increasing height was continuing [Chinn and Rona 1984, Butler et al 1987, Voss et al 1987, Chinn et al 1989]. In light of these findings, a large-scale project was undertaken in 1991 to produce new reference data for the UK. This project used current data that were nationally representative and resulted in the introduction of the 1990 UK growth standards [Freeman et al 1995, Cole et al 1995]. Since their introduction, it has been demonstrated that these standards are appropriate for today's children [Cotterill et at 1996, Mulligan et al 1998] and so have been retrospectively adopted for use throughout this thesis. Thus, the short children in the Wessex Growth Study, identified on the basis of outdated standards, were even shorter by today's standards and all had a height that was somewhat less than the current 3rd centile.

Another reason why growth standards may not be appropriate is ethnicity [Eveleth and Tanner 1990]. It is well documented that height and weight varies from one human population to another. For example, the mean height of well-nourished Japanese males falls almost 13cm below that of those from the Netherlands while American males, though slightly shorter than their Dutch compatriots are, in fact, heavier [Bogin 1988]. Environmental factors contribute significantly to growth and development and some of the difference in body size between races is a direct result of differing living conditions. In the early 20th century, Boas found that children of immigrants to USA became taller and heavier than their parents and that the longer the childhood exposure to an improved environment, the greater the physical difference. Nevertheless, the mean height of Asiatic children living in Britain, even after several generations, is somewhat less than the UK population standard [Rona and Chinn 1986], highlighting the importance of genetic inheritance. Many studies, reviewed by Eveleth in 1986, have also shown that ethnicity affects both the tempo of growth, as measured by skeletal maturity, and, using age at menarche as a proxy, pubertal development. For all of these reasons, those of ethnic origin whose first language was not English were excluded from this study.

Many pathological conditions, both congenital and acquired, are associated with short stature [Parkin 1976]. These include endocrine disorders, such as growth hormone deficiency and hypothyroidism, and specific syndromes, including Turner, Noonan and Down's. Growth, however, is thought to be a sensitive indicator of a child's well-being [Parkin 1976] and most chronic systemic disease causes poor growth leading to short stature, for example asthma, renal disease, congenital heart disease, cystic fibrosis and coeliac disease [Lipman and McKnight 2000]. The prevalence of short stature associated with organic disease is estimated to be approximately 1 in 500 [Macfarlane 1995]. Although most cases will have other presenting symptoms, short stature is, at times, the only outward sign of pathology and growth screening is useful in identifying the already short child with 'silent' pathology [Lacey and Parkin 1974a, Vimpani et al 1981, Voss et al 1992]. These studies have also demonstrated that as stature decreases, the probability of a pathological explanation increases. Some years ago, Lacey and Parkin (1974a) found that 16% of children whose height was less the 3rd centile, equivalent to a standard deviation score of -1.9, had organic disease to explain their short stature but that this incidence rose to 69% for those with a height more than 3 standard deviations below the mean. These findings have been confirmed and it is likely that approximately 1 in 5 very short children will have organic disease. Most

pathology is identified before school entry, but referral for specialist opinion of short, apparently healthy, children is likely to reveal further new cases.

To exclude undiagnosed pathology, the short children in the Wessex Growth Study underwent a blood test to measure haemoglobin concentration, urea, electrolytes and thyroxine, and also an X-ray of the left hand and wrist for an estimation of bone age, using the RUS-TW2 method [Tanner et al 1983b]. Those children for whom test results were abnormal or pathology suspected were then examined by a paediatrician, which revealed seven children with pathology. It was not ethically possible to test the growth hormone status of all the apparently normal, short children. However, during the course of the first 18 months of follow-up, a timed, overnight urine specimen was collected from 64 children. These children were representative of the total sample with respect to height, and analysis of the rate of urinary GH excretion was within normal limits. Moreover, continued monitoring has not revealed any new cases of growth related pathology.

A delay in skeletal maturity is not necessarily an indication of pathology. Indeed, many short normal children, referred to growth clinics are found to have a delayed bone age [Rekers-Mombarg et al 1996]. Delayed maturation is even more likely if these children are short for parents. The primary aims of this thesis are to determine final height outcome and to find genetic and environmental predictors of adult stature. Consequently, regardless of their skeletal maturation or parental target height, all short children with no evidence of pathology were considered eligible for recruitment to the Wessex Growth Study. From a population of 14,346 children, 142 were identified as 'short normal', that is with a height below the 3rd centile according to Tanner and Whitehouse standards and with no pathology to explain their short stature. Of these, 140 (76 boys, 64 girls) agreed to participate.

1.11 Summary

Short adults are reported to have greater psychological and health risks but not all very short children will become very short adults. Adult stature is the culmination of foetal, infant, childhood and pubertal growth and, within each phase, individuals vary in both the rate of maturation and intensity of growth. To a large extent, both stature and the tempo of growth are genetically determined but many social and environmental factors can have a modifying effect. Poor environmental conditions can cause growth to falter but equally an improvement in quality may result in catch-up growth.

Between 10 and 30 cm of adult height is a result of pubertal growth. Poor growth during puberty will result in a short child becoming a very short adult. Consequently, accurate prediction of pubertal growth would provide a valuable tool for the assessment of short stature in the prepubertal short normal child.

The Wessex Growth Study is a longitudinal study of the growth and development of an unselected population of short normal and average height control children recruited as they entered primary school and followed until final adult height. All short but otherwise healthy children in a well-defined but wide geographical area were included and there were a similar number of boys and girls. Each short normal child was age- and gender- matched with a control child of average stature. As well as measurements of height and weight, a great deal of background information, which included parental heights, birth history, social & family background, and medical history, was also collected for each child.

The aims of this thesis are:

(iii) to examine the patterns of growth and final height outcome of short normal children in a community setting and to compare these with children of average height.

(iv) to assess the impact of biological and environmental parameters on final height outcome.

Chapter 2: SUBJECTS AND METHODS

It is undoubtedly true that short parents generally have short children while tall parents have tall children. Nevertheless, while parents may well supply the goal, many paths lead to that goal. While some children rush to the finishing tape and others dally by the wayside, some steer off-course. This chapter describes the methods used to estimate deviation from the 'goal', or genetic potential, and the methods used to assess the path of growth from recruitment at school entry through puberty until the attainment of final height. A review of the recruitment procedure to the Wessex Growth Study is also included.

2.1 Recruitment to the study

The Wessex Growth Study is a longitudinal, cohort study monitoring the physical growth and psychological development of short normal and average height children in the community. Children were recruited from two adjacent health districts, Winchester and Southampton, in the Wessex Health Region. This area has a low population turnover and is within a 30-mile radius of Southampton General Hospital, the study centre. Children were selected on the basis of their height at the school entry medical when they were aged between 4-6 years. Approval for the study was given by the hospital Ethical Committee and agreed with the Hampshire Education Authority before writing to the headteacher of all local authority primary schools outlining the study objectives. Meetings were held with all Clinical Medical Officers, School Nurse Managers and school nurses to enlist their cooperation and assistance.

Short Normal Subjects

When the Wessex Growth Study was established in 1986, the current UK standards were those of Tanner and Whitehouse [Tanner et al 1966a, 1966b] and short stature was considered to be below the bottom line on these height charts, that is the 3rd centile. All school nurses serving the local authority primary schools were asked to refer any child entering school in 1985/86 and 1986/87 whose height was near or below this cut-off point, including those with known organic disease. These children were referred to an experienced auxologist (LV) who verified age and height measurement and retained all those confirmed by this measurement to be on or below the 3rd centile by these standards, equivalent to a height standard deviation score of –1.85 or less. A total of 14,346 children were screened and 180 (97 boys, 83 girls) were found to have such an extreme height centile. Twenty-five of

these children were already known to have pathology that might explain their short stature [Voss et al 1992].

In order to rule out undiagnosed pathology, the short, apparently normal children underwent a blood test to measure haemoglobin concentration, urea, electrolytes and thyroxine, and also an X-ray of the left hand and wrist for an estimation of bone age, using the RUS-TW2 method [Tanner et al 1983b]. All bone age assessments were made by a single trained auxologist (LV). Those children for whom test results were abnormal or pathology suspected were then examined by a paediatrician which revealed a further seven children with pathology.

It was not ethically possible to test the growth hormone status of all the apparently normal, short children. However, during the course of the first 18 months of follow-up, a timed, overnight urine specimen was collected from 64 children. These children were representative of the total sample with respect to height, and analysis of their rate of urinary GH excretion was within normal limits [Wilkin et al 1992].

From the 180 children verified to have a height below the 3rd centile, those with known pathology (n=25) and the new diagnosed cases with pathology (n=7) were excluded from the study. A further six children from immigrant families for whom English was not the first language were also excluded as ethnicity is known to affect height, even after several generations [Rona and Chinn 1986]. Parents of the remaining short normal children were asked for written consent allowing their child to be measured in school. The parents of only two children refused consent leaving 140 (76 boys, 64 girls) short normal (SN) children to be recruited into the Wessex Growth Study.

Control Subjects

To ensure homogeneity with respect to age and gender, each short normal child in this cohort study was matched with a control (C) of the same gender and in the same school class. A primary aim of this study was to compare the patterns of growth of short normal children to those of *average* height. In this context, average height should not be taken as the mean population height but rather a height within the average range, thus children who could be considered tall or short were excluded. Consequently, the same sex child nearest in age to the study child whose height was between the 10th and 90th centile according to Tanner and

Whitehouse standards was selected. Permission was obtained from parents before recruitment who confirmed that, at that time, the control child had no known health problems.

Longitudinal follow-up

The Wessex Growth Study is a longitudinal, cohort study that has been ongoing for some 16 years. During this time, height and weight have been measured regularly and parents of both short and control children have been re-interviewed. Longitudinal monitoring has not revealed any further cases of pathology among the short children, but, during the pubertal years, 3 (2 girls) control children developed diabetes and 1 control girl hypothyroidism. After diagnosis, these children were excluded from further analyses.

2.2 Social and Medical History

Both parents of the short normal children were invited to attend an initial interview at school in order to provide details of family and social background, including ethnic origin, marital status, family structure and social class. Social class was based on the father's occupation and coded according to Registrar General's Classification of Occupations. A medical history of the child was also taken to include birth history, acute and recurrent infections and atopic (asthma and eczema) disease. Parents who attended were measured otherwise an estimate of height was obtained from self or partner. One or both parents of 136 short normal children were interviewed and measured height was obtained for 116 mothers and 50 fathers. Parents who did not attend were sent postal questionnaires asking for these details.

The parents of the control children were not interviewed, but were asked to complete a short postal questionnaire detailing family structure, social background, and medical history. Parents were also asked to report their heights. Non-responders were sent further questionnaires and, if necessary, a telephone follow-up resulting in a response rate of 132 (94%) completed questionnaires. From these questionnaires, estimates of heights were obtained for 131 mothers and 124 fathers of the control children.

Later, during 1994-95, the parents of both short and control subjects were asked to participate in a semi-structured interview. This was to obtain detailed sociological data allowing the family structure and socio-economic conditions prevalent through pubertal development to be determined. The interviews were conducted shortly after the participants entered secondary school when they were aged between 12-13 years. Some sample attrition had occurred with

13 short normal and 21 control subjects being lost to follow-up. In addition to providing information on the family structure, housing and income, parents were also asked to provide details of their educational attainment and employment history. For many of the subjects, socio-economic circumstances had changed since recruitment and social class was therefore re-evaluated using the occupational status of the chief income earner in the household at that time, according to the Market Research Society (1991) classification. This interview also provided the opportunity to verify and update details of the child's birth and medical histories. In particular, the presence and treatment of atopic disease was noted. As well as asthma and eczema, atopic disease was now considered to include hayfever and allergy.

2.3 Genetic Height Potential

Two methods are commonly used to judge if a child's height is appropriate for parents [Ranke 1996, Schilg and Hulse 2000]. The parent-specific method (equation 1) uses mid-parental heights to determine the expected height centile range of a couple's children [Ranke 1996], and can be applied using Tanner's parent-allowed for charts [Tanner et al 1970]. The adult height potential method (equations 2 & 3) uses the parents' height to calculate their children's likely adult height range [Schilg and Hulse 2000], which may then be converted to standard deviation scores using the appropriate standards. With both methods, a child whose current height centile lies below the expected or target range is judged to be inappropriately short and classified as having non-familial short stature (non-FSS).

$$targetrange = r_1 * \left[\frac{mother'sHSDS + father'sHSDS}{\sqrt{2(1+r_2)}} \right] \pm 2\sqrt{1-r_1^2} \quad \text{sds} \qquad (1)$$

where r_2 is the correlation between parents' height, which is 0.3 [Ranke 1996], and r_1 is the correlation between the child's height and mid-parental height, which is 0.5 between the ages of two and nine years [Ranke 1996].

BOYS: $$targetrange = \left[\frac{father'sheight + mother'sheight}{2} + 7 \right] \pm 10 \quad \text{cm} \qquad (2)$$

GIRLS: $$targetrange = \left[\frac{father'sheight + mother'sheight}{2} - 7 \right] \pm 8.5 \quad \text{cm} \qquad (3)$$

The parent-specific method allows for regression towards the mean, as described by Galton [1886], and is considered to be more appropriate for children of short stature [Ranke 1996]. Nevertheless, as this method depends on the correlation between the heights of parents and their prepubertal children, it is, strictly speaking, valid only for children between the ages of two and nine years [Tanner et al 1970]. On the other hand, the adult height potential method is intended to be used in conjunction with the child's predicted ***adult*** height [Tanner 1986]. Thus, evaluating a child's height with this method assumes that the height centile will not significantly deviate during childhood growth. However, this is unlikely to be the case for many children as the correlation between a child's height at age five and subsequent adult height is somewhat less than 1 [Tanner et al 1956].

Neither method allow for the tempo of growth even though there is evidence to suggest that short normal children whose bone age is delayed are likely to achieve significant catch-up growth and attain an adult height within target range [Crowne et al 1990 1991, Sperlich et al 1995, Ferrandez et al 1996].

Although both methods have advantages and disadvantages, it was considered that the adult height potential method (equations 2 and 3) should be used throughout the course of the study, as this would allow catch-up growth, if any, to be monitored.

2.4 Predicted Adult Height

An X-ray of the wrist and left-hand was available for 119 (65 boys) short normal children. Most of these had been obtained shortly after recruitment but 7 children had already undergone the procedure prior to recruitment. The X-rays were used to assess bone age by a single trained observer (LV) using the RUS-TW2 system [Tanner et al 1983b].

Predicted height was calculated using the TW Mark II prediction equations, which are suitable for boys from the age of 6 years and girls aged 5 years and over. At the time of the X-ray, all children were prepubertal and aged between 4 and 8 years (mean age 5.76yr). For boys aged 6 years and over (n=19), and girls aged 5 years and over (n=51), the corresponding bone age, chronological age and height measurement were used to calculate predicted adult height using the appropriate TW Mark II height prediction equation, [Tanner et al 1983b]. For the remaining 46 boys and 3 girls, predicted height was estimated using the height measurement nearest the age of 6 and 5 years, respectively. In these cases, bone age was

calculated assuming the same difference between chronological age and bone age as at the time of the initial x-ray. The mean difference between the age at initial bone age assessment and that used to predict adult height was 0.83 years.

2.5 Growth Data

Until the subjects left compulsory education at the age of 16 years, heights and weights were measured in school by a single trained observer (LV) at six-monthly intervals. Thereafter, measurements were made at home and continued to be collected every six months until the completion of puberty and annually thereafter. During this time, a changeover of the trained observer occurred (JM).

Height was measured using the standard technique as described by Cameron (1986) and recorded to the nearest millimetre. Even experienced auxologists have recorded significantly different mean heights when measuring the same group of children [Voss et al 1990, Voss and Bailey 1994]. Consequently, when trained observers were changed, care was taken to ensure both used the same measurement technique with similar precision. For each observer, the error of measurement, expressed as the standard deviation of a single height measurement, was found to be approximately 0.25cm. During the first five years, measurements were made using the Holtain electronic stadiometer, which was then replaced with the more portable Leicester height measure. Error is inherent in measuring height but the major source of variance is from the child [Voss et al 1990]. Indeed, inexpensive, portable instruments, properly installed and calibrated, are just as reliable those used in growth clinics [Voss and Bailey 1994]. To ensure further precision, height was recorded as the mean of three measurements. Height data was used to calculate annual height velocities.

At each visit, weight in light clothing was recorded on a set of self-calibrating electronic scales accurate to within 100g. No adjustment was made for clothing. Weight at all ages is considered to be a reliable anthropometric measurement with low intra- and inter-variability [Ulijasek and Kerr 1999]. Although weight does fluctuate during the day, very little variation can be attributed to either the observer or the instrument.

Height and weight measurements were used to calculate body mass index (BMI) according to the formula weight(kg)/height(m)^2.

In order to make comparison between children of different sexes and ages, all height, weight and BMI measurements were converted to standard deviation scores. The children were recruited to the study on the basis of their height standard deviation score calculated according to the standards of Tanner and Whitehouse. However, in light of the continuing secular trend in height [Chinn and Rona 1984, Voss et al 1987], new UK growth standards were introduced in 1995, which were considered more appropriate for children of the 90's [Freeman et al 1995, Cole et al 1995]. Consequently, all height, weight and BMI measurements made throughout the study have been converted to standard deviation scores using the LMS method [Cole 1989] and these new standards.

2.6 Prepubertal Growth

The growth of the short normal and control children was examined over a full three-year period between the ages of six and nine years. Although all children were measured as far as possible at approximately six monthly intervals, this was not done at any specific age points and, inevitably, some had missing measurement. Moreover, control children were recruited some six months after the short children and so fewer had been measured before the age of six. Between the ages of 1 to 10 years, height can be fitted by a curve of the form $y=a + bt + c\log t$ [Sinclair 1989]. However, the term $c\log t$ is small [Israelsohn 1960] such that in mid-childhood, between the ages of 5 to 9 years, when height velocity is at its most constant (see figure 1.4), the growth curve of the prepubertal school child approximates a straight line of the form:

$$height=m*age+k \qquad where \;\; m=gradient\ of\ the\ line\ and\ k=constant$$

Consequently, a regression model was fitted to the heights of all children who had been measured for at least two years before puberty. To ensure as far as possible parity between the groups, no height measurements before the age of 5.5 years were used. Estimates of m and k were obtained for each child and used to calculated height at age 6 and 9 years (figure 2.1). As error is inherent in measuring height, this method has the added advantage of dampening the effect of this error. To allow comparison between the sexes, these heights were converted to standard deviation scores. The prepubertal change in height SD score was calculated by subtracting height SD score at age 9 from that at age 6 years.

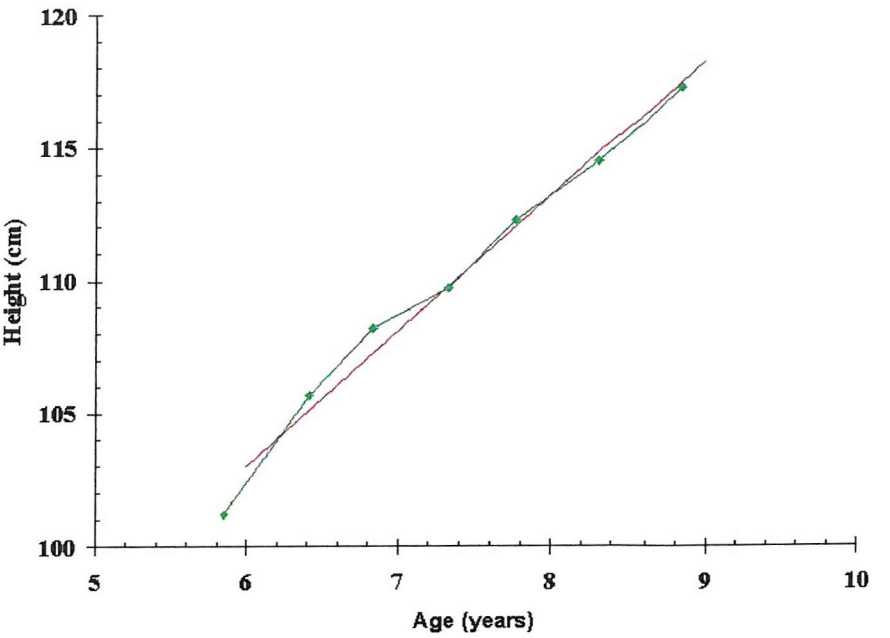


Figure 2.1 *A regression model was fitted to the prepubertal heights of each short and control child and height at the ages of 6 years and 9 years were estimated*

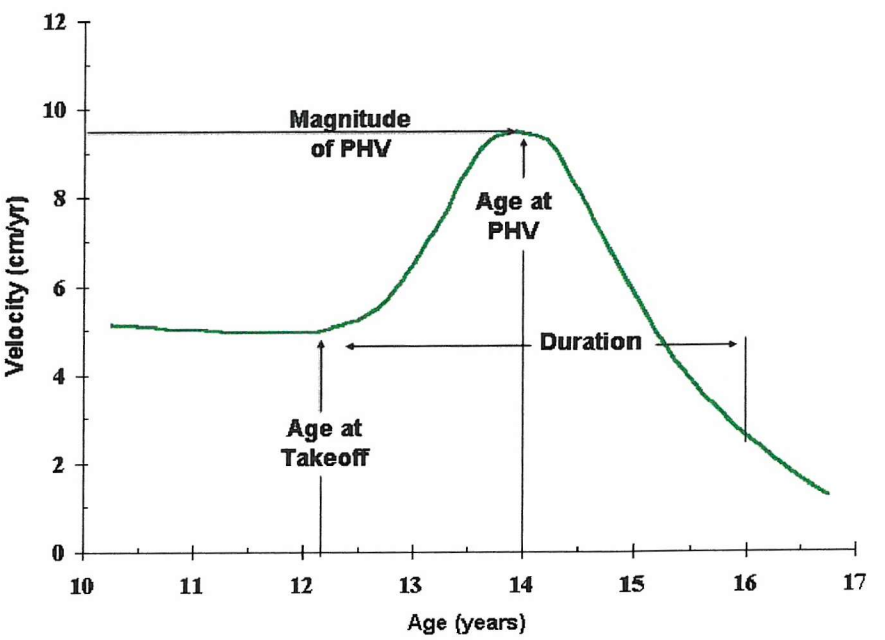


Figure 2.2 *A typical pubertal growth spurt and pubertal parameters*

2.7 Pubertal Growth

For both males and females, pubertal growth can be defined by four main parameters: the age at take-off in height velocity, the age at peak height velocity (PHV), the magnitude of PHV and the duration of puberty (figure 2.2). Estimates of these 4 parameters were calculated for each child using the annual height velocities and the methods detailed below.

Age at take-off

The age at take-off is the point just before puberty begins when the rate of growth reaches its lowest point. In theory, this can be detected on the height velocity curve but in practice the error inherent in measuring height means that height velocity cannot be expressed with sufficient precision for this purpose [Taranger and Hagg 1980, Voss et al 1991b]. In order to dampen some of the variation due to measurement error, individual height velocity curves were re-drawn after taking 3-point moving averages calculated using the following method:

For each height velocity curve with $vel_1, vel_2, \ldots, vel_n$ occurring at $age_1, age_2, \ldots, age_n$, the average velocity and average age at each time point was calculated according to the formulae

$$avevel_i = \frac{vel_{i-1} + vel_i + vel_{i+1}}{3}, \quad average_i = \frac{age_{i-1} + age_i + age_{i+1}}{3}$$

This resulted in a smoothing out of the height velocity curve as illustrated in figure 2.3 giving a clearer picture of the underlying trend. A computer program was then used to detect the nadir of velocity preceding the peak. Each curve was then visually inspected to ensure the accuracy of the computer selected data and adjustments were made if necessary.

Age and magnitude of Peak Height Velocity

An assumption was made that the data points around the peak value of the pubertal height velocity spurt had a quadratic form. The magnitude and age at peak height velocity (PHV) were estimated using the simple device of fitting a parabola of the form:

$$Velocity = b_0 + b_1(age - b_2)^2 \qquad where\ b_0 = magnitude\ of\ \text{PHV},$$

$$b_1 = gradient\ of\ curve\ around\ the\ peak,$$

$$b_2 = age\ of\ \text{PHV}$$

to a maximum of five observed velocities around the observed peak (figure 2.4). Estimates of b_0, b_1, and b_2 were found by least squares.

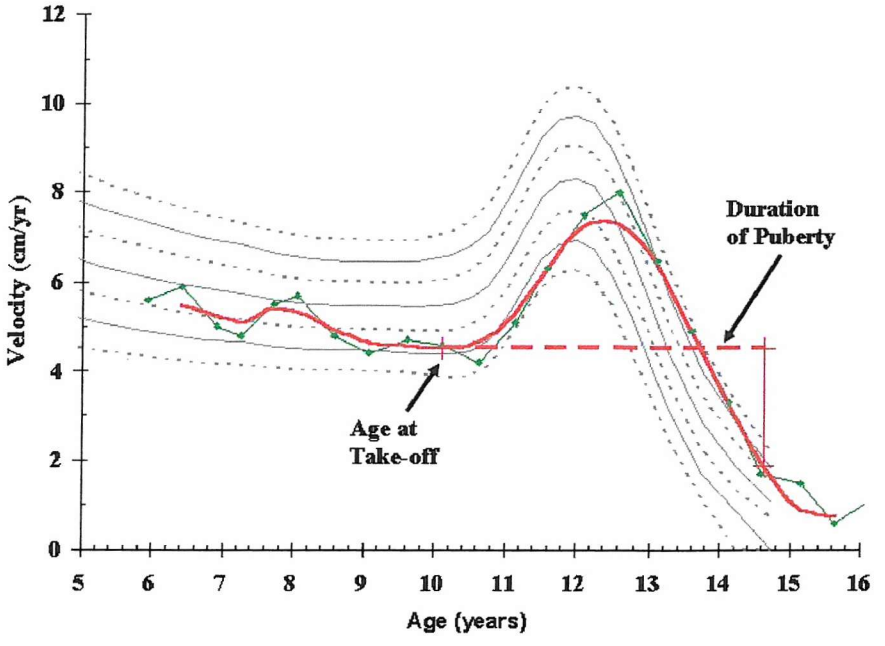


Figure 2.3 *Age at take-off and the duration of puberty were found after smoothing the height velocity curve by taking 3-point moving averages*

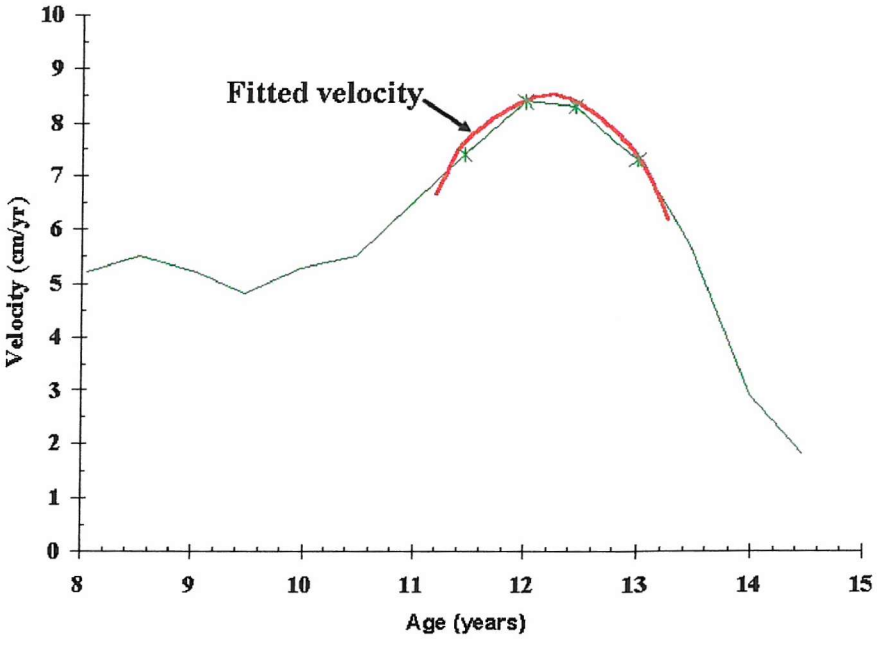


Figure 2.4 *The magnitude and age at PHV were estimated by fitting a parabola around the observed peak*

Height velocity curves are peculiar to the individual and so selection of the data points used for obtaining the estimates was somewhat subjective. Selection of these points was first of all made by a computer program written to detect the pubertal peak velocity. Each height velocity curve was then studied individually to ascertain the appropriateness of these computer-selected points and adjustments were made if necessary. For some children, the variation of height velocity during the pubertal period made detection of the peak difficult. In these cases, the height velocity curve was smoothed using the 3-point moving average technique and the resultant curve re-evaluated. This method clarifies the peak allowing the most appropriate data points to be selected. An illustration of the improvement made by 3-point moving averages is shown in figure 2.5.

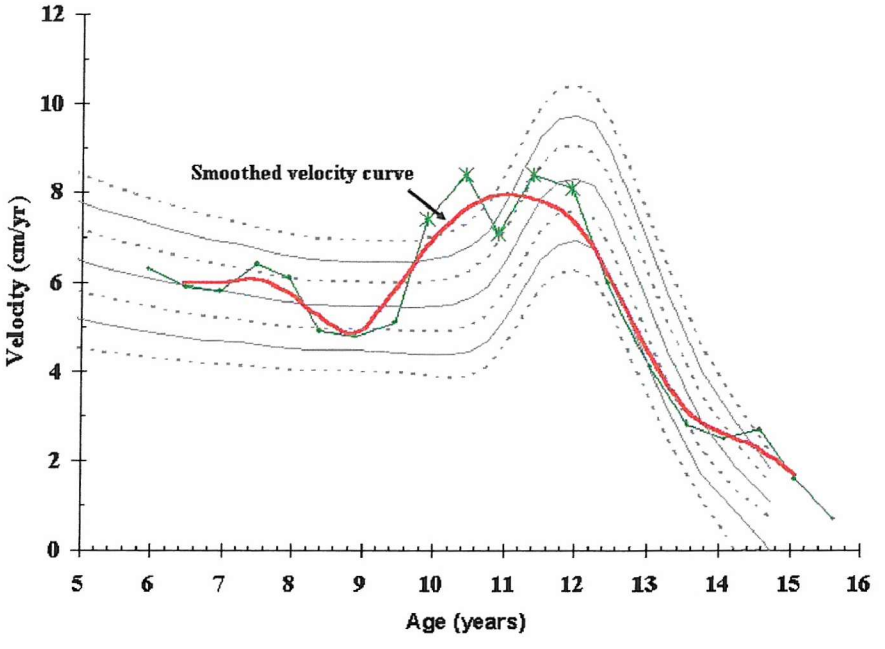


Figure 2.5 *After smoothing the velocity curve using 3-point averaging, points marked by * were chosen to estimate age and magnitude of PHV*

The duration of puberty

The duration of puberty is considered to be the time taken from the start of the pubertal spurt until the attainment of adult height. In practice, the error inherent in measuring height makes the identification of final height difficult to determine [Kato et al 1998]. Consequently, various definitions defining the end of puberty have been used [Tanner et al 1976, Largo et al 1978, Taranger and Hagg 1980, Gasser et al 1985, Tanaka et al 1988, Buckler 1990]. Most

authors have based this on some arbitrary average annual growth rate. For example, Largo et al (1978) have defined the end of the spurt as the age when growth rate has returned to the minimum prepubertal velocity, a value that varied between 3 and 4.5 cm/yr, whereas Taranger and Hagg (1980) chose the age of the first annual increment below 2 cm/yr. The method of Largo et al was considered unsuitable for the present study. During the prepubertal phase of growth short children growth at a slower rate than those who are taller [Bailey 1994], thus such a definition may produce bias when comparing groups of quite different heights. Other definitions have also been used. Gasser et al (1985) chose not to use velocity but instead used the age of maximal deceleration as the end of puberty, Buckler (1990) used the age at which 95% of final height was attained, and Tanaka et al (1988) chose a definition that combined age and velocity.

In this study the duration of puberty was estimated, again somewhat arbitrary, from the smoothed velocity curve as the time taken to achieve a velocity <3cm/yr after take-off occurred (figure 2.3). Until this time, all participants had been measured at 6-monthly intervals and there was a continuous marked decrease in the growth rate.

The adolescent height gain

Once age at take-off and age at completion of the spurt had been estimated, the adolescent height gain was determined for each child. First, the height at each of these ages was calculated using the longitudinal height measurements and interpolating between the two nearest 6-monthly measurements if necessary. The adolescent height gain was considered to be the difference between these two heights.

2.8 Final Height

After the participants of the Wessex Growth Study left compulsory education, measurements were made at home and it became increasingly difficult to ensure 6-monthly measurements. In this now teenage population, appointments were likely to be forgotten and diurnal variation in height was also more noticeable, ***even*** with afternoon measurements. Height is not an exact measure [Voss et al 1991b] and as the rate of growth decreases, the relative influence of measuring errors increases. These errors make the precise age when growth ceases difficult to determine. As a result, studies investigating the growth and development of children have employed many different definitions of final height. These have been based primarily on the study design and include age [Sperlich et al 1995, Greco et al 1995, Patel et

al 1997], height velocity [Crowne et al 1990 1991, Bernasconi et al 1997], skeletal maturation [Volta et al 1988, Hibi and Tanaka 1989] or a combination of all these factors [Hindmarsh and Brooke 1996]. Few of these criteria, however, can provide a definitive final height. Measurement error makes velocity problematic and, even after epiphyseal, stature continues to increase [Garn 1961, Roche and Davilla 1972]. In a longitudinal study, such as this, specifying a universal 'adult' age is impractical [Roche 1984]. While some girls have completed their growth before the age of 16 years, some boys continue to grow into their twenties [Roche and Davilla 1972]. To a large extent, however, age when growth ceases depends on the timing of puberty. In this study, final height therefore has been taken as the last measurement made ***provided*** this was at least 3 years after PHV or, in the case of girls, 2 years after menarche if PHV was not available. By this time, height velocity had decreased below 2cm/yr.

2.9 Sample Attrition

Some sample attrition is inevitable in a prospective cohort study. Children were lost to follow-up for a number of reasons. As mentioned in 2.1, four control children developed endocrine pathologies but most children were lost to follow-up simply because they moved without giving a forwarding address. This was particularly the case during the transition to adulthood as the young people moved from schools to the workplace and became more mobile. With assistance from schools and GPs, attempts were made to trace and, where possible, re-instate these children though some missed measurements inevitably occurred.

The largest single loss occurred in 1989, some three years into the study, when 20 (10 boys) of the shortest children in the short normal group were recruited to a trial of growth hormone therapy and received treatment [Walker et al 1990]. Although these children were statistically shorter at recruitment than the remaining SN children, this difference was not considered to be clinically significant. Moreover, in all other respects they were typical of the short normal school entrant (table 2:1).

Table 2:1 *Comparison of the 20 short normal children recruited to a trial of growth hormone therapy with the remainder of the cohort*

	REMAINING SN			GH TREATED			
	Mean	**SD**	**N**	**Mean**	**SD**	**N**	***p-value***
Recruitment height SDS	-2.69	0.33	120	-2.94	0.43	20	*0.003*
Bone age SDS	-0.71	0.94	98	-0.56	1.12	20	*0.510*
Predicted height SDS	-2.10	0.59	98	-2.36	0.68	20	*0.079*
Birth weight SD	-0.90	1.14	114	-0.94	1.39	20	*0.891*
Target height SD	-1.45	0.66	115	-1.72	0.62	20	*0.098*
Target – Initial Ht SD	-1.24	0.72	115	-1.22	0.67	20	*0.900*
Gender							
male			66 (55%)			10 (50%)	*0.809*
female			54 (45%)			10 (50%)	
Social Class							
I & II			23 (23%)			1 (5%)	*0.192*
III(a) & III(b)			48 (47%)			12 (60%)	
IV & V			31 (30%)			7 (35%)	

This thesis is concerned with the analysis of the data at four specific phases: recruitment, prepubertal growth, pubertal growth and final height. Figure 2.6 summarizes the sample size and attrition during the course of the study.

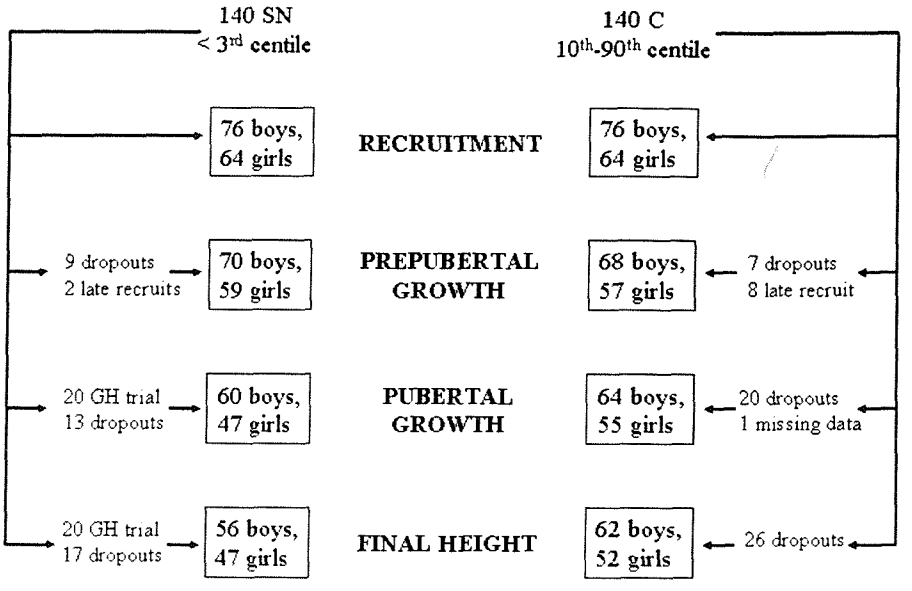


Figure 2.6 *School entry height screening identified 140 SN children who height was less than Tanner's 3rd centile but during the course of the study sample attrition occurred as illustrated above*

At recruitment the cohort consisted of 140 (76 boys) SN and 140 (76 boys) C children. Only children whose height had been measured for at least two years between the ages of six and nine years were considered eligible for the analysis of prepubertal growth. At this time, 16 (7 controls) were lost to follow-up and 10 (8 controls) whose first measurement was recorded after the age of seven were excluded.

Pubertal growth is characterised by peak height velocity and, in the case of girls, menarche. All girls who reached menarche where included in the analysis of pubertal growth and all boys whose height measurements obtained during adolescence were sufficient to define age and magnitude of the peak. This resulted in the exclusion of 33 SN and 21 C children. The 33 SN children included the 20 children recruited to the growth hormone trial.

A final height measurement was available for 103 SN and 114 C children.

2.10 Statistical Analysis

The data has been analysed throughout this study using the statistical package SPSS. Student's t-test and one-way analysis of variance were used to compare means, and Chi-square to compare categorical data. Analysis of covariance (ANCOVA), and multivariate analysis of variance (MANOVA) have been used where appropriate Stepwise multiple regression was used to determine predictors of stature and pubertal development.

In a longitudinal cohort study, such as this, the data will be variably complete at different time points and consequently study numbers in figures, tables and appendices will vary slightly. However, as the cohorts consist of relatively large numbers, the missing data is unlikely to influence the overall results.

Chapter 3: GROWTH BEFORE PUBERTY

Nature and nurture both play a role in the growth and development of a child. Stature may well be an inherited characteristic, but, to achieve optimum growth, a child must be healthy, well-nourished and reared in a caring environment. The interaction of genes and the environment can best be observed in the prepubertal years when growth is steady and predictable and there is little difference between the sexes. This chapter seeks to examine the interaction of genes and environment and their role in the control of growth.

3.1 Introduction

Over 100 years ago, Franz Boas (1897) observed that while all children pass through the same developmental milestones, some did so more slowly than others. He termed this the *'tempo of growth'*. He noted that those with a slow tempo of growth were shorter throughout childhood than those with a rapid tempo but that slow growers tended to have a delayed pubertal spurt and continue to grow for longer. Boas demonstrated that the rate of development was affected by heredity, nutrition, social circumstances and by the interactions of all these factors. Since then many studies have confirmed that growth is a continuous and complex interaction between genes and the environment.

Dental maturity and skeletal maturity are measures of physiological maturation rate [Tanner 1989, Sinclair 1989] and there is evidence to suggest that short normal children, like those recruited to the Wessex Growth Study, are likely to have a slow tempo of growth. Several studies have reported that dental maturity is delayed in children with short stature [Krekmanova et al 1997, Kjellberg et al 2000], while many short but otherwise healthy children referred to growth clinics are found to have a delayed bone age [Albanese and Stanhope 1995]. It is also likely that many short normal children do ***not*** become short normal adults. Follow-up of a national population sample found that two out of three short normal prepubertal children achieved an adult height within the normal range [Greco et al 1995]. Moreover, children referred to growth clinics and diagnosed with constitutional delay of growth and puberty (CDGP) are consistently reported to achieve spontaneous catch-up growth resulting in a final adult height appropriate for parental target range [Crowne et al 1990 1991, Sperlich et al 1995, Ferrandez et al 1996].

To a large extent, stature and maturation are genetically determined. Twin studies clearly demonstrate the hereditary nature of these variables [Wilson 1986a 1986b, Preece 1996, Beunen et al 2000]. Parental height is a strong predictor of both childhood and subsequent adult stature [Goldstein 1971, Rona et al 1978, Kuh and Wadsworth 1989]. In a study of over 9000 children, Rona et al (1978) confirmed parental height to be the most important factor, responsible for the majority of the explained variation in attained height. Similarly, long-term follow up of the 1946 birth cohort involving over 3000 adults found that 26% of the variance in male and female adult height was explained by the variance in parental heights [Kuh and Wadsworth 1989]. Nevertheless, these studies and others have also found that the environment in which a child grows up exerts considerable influence. In one community study in Newcastle, poor social conditions were found to contribute to the growth and development of at least one third of short, apparently healthy, children [Lacey and Parkin 1974b] with low social class, long-term unemployment and poor parental care playing a critical role. Vimpani et al (1981) also found one-third of short normal children in Scotland to be severely socially disadvantaged while a more recent Scottish study has also confirmed an association between urban deprivation and height [White et al 1995].

These detrimental associations between height and social factors, however, appear to be restricted to the pre-school years. Longitudinal data from the National Study of Health and Growth (1972) show that although school-age children living in deprived circumstances are shorter than might be expected, the height differences between social groups remained stable at least during the primary school years [Smith et al 1980]. Further reports from the same study confirmed these findings and argued that in early childhood, before the age of 3 years, children are vulnerable to deprivation but become more resilient as they grow older [Rona and Chinn 1981]. A study examining the effects of social deprivation on skeletal maturation supports this hypothesis [Cole and Cole 1992]. On examining the radiographs of over 1500 children aged 0-19 years, highly significant negative associations were found between skeletal maturity and social factors such as unemployment, single parent families and overcrowding. Regardless of their chronological age, children living in difficult social circumstances had similar bone age deficits, suggesting that deprivation retarded skeletal maturation during a critical period in early life. Indeed, the pattern of growth in the first three years of life is considered to be crucial for subsequent long-term growth and it is uncertain if adverse influences in this period are fully reversible [Buckler 1994].

Although short parents tend to produce short children, it is clear that to achieve their height potential, children must not only be well-nourished and healthy but be reared in a caring environment. The short normal children in the Wessex Growth Study may simply have inherited short stature or it may be that their height had already been compromised by poor social conditions. This chapter seeks to examine the influence of genetic and environmental variables on childhood stature and to examine the interaction of these variables and determine their role in the control of growth.

3.2 Genetic profile at recruitment

As described in the previous chapter, 142 short normal children were identified at school entry and 140 (76 boys) agreed to participate in the Wessex Growth Study. Each child was then age- and gender- matched with a child in the same school class whose height was within the expected range. When the first measurement was taken, the mean age of the short normal (SN) subjects was 5.61 years while that of the controls (C) was slightly later at 6.03 years. At recruitment, parents provided information on their child's health and social background. A summary of the genetic, social, and environmental profile of the short normal children and their controls is shown in Table 3:1. All growth data has been converted to standard deviation scores (SDS) using the 1990 UK growth standards [Freeman et al 1995, Cole et al 1995] to allow comparison between the sexes and at different ages.

Height, weight and body mass index

The mean height of the short normal children at recruitment was close to the 0.4th centile with all having a height below the 2nd centile. By comparison, the mean height of the control children lay on the 42nd centile and ranged from the 6th to the 90th centiles. Although the mean weight centile was similar to the mean height centile for both short and control groups *(SN: 0.6th centile, C: 37th centile)*, the mean BMI of the short normal children was significantly lower than that of the controls.

For the short normal group, there were no significant gender differences for height *(boys: -2.71, girls: -2.74, p=0.684)*, weight *(boys: -2.62, girls: -2.38, p=0.100)* or BMI *(boys: -0.77, girls: -0.67, p=0.558)*. Compared to the control boys, the control girls tended to be shorter *(boys: -0.04, girls: -0.38, p=0.001)* and lighter *(boys: -0.21, girls: -0.50, p=0.050)*, but both had similar BMI *(boys: -0.33, girls: -0.42, p=0.573)*.

Table 3:1 *Profile at recruitment of the 140 short normal and 140 control children in the Wessex Growth Study. The table shows mean (SD) for continuous variables and number (%) for categorical variables. Data for some children was incomplete as indicated by the values of N.*

	SHORT		CONTROL		
	Mean (SD)	**N**	**Mean (SD)**	**N**	***p-value***
Genetic profile					
Age (years)	5.61 (0.40)	140	6.03 (0.62)	140	<0.001
Height SDS	-2.72 (0.35)	140	-0.20 (0.62)	140	<0.001
Weight SDS	-2.51 (0.82)	133	-0.34 (0.87)	140	<0.001
BMI SDS*	-0.73 (0.96)	133	-0.37 (0.97)	134	0.003
Birth weight SDS*	-0.90 (1.18)	134	0.10 (1.17)	136	<0.001
Mothers' Height (cm)	154.5 (5.2)	138	162.6 (5.6)	136	<0.001
Fathers' Height (cm)	168.3 (7.0)	135	177.4 (6.9)	129	<0.001
Target Height SDS	-1.49 (0.66)	135	-0.14 (0.65)	129	<0.001
Child SDS-Target SDS	-1.24 (0.71)	135	-0.08 (0.71)	129	<0.001
Bone Age SDS*	-0.69 (0.97)	118			
Predicted Height SDS	-2.15 (0.61)	118			
Birth history					
Maternal age (years)*	24.9 (4.6)	113	25.0 (4.3)	113	0.933
Low Birth weight (<0.4)	15 (11%)		0		<0.001
Gestational Age (weeks)	38.9 (2.0)	137	39.2 (1.5)	137	0.226
Premature (≤ 36 wks)*	17 (12.4%)		13 (9.5%)		0.562
Birth Order*					
First born	49 (35.3%)		62 (44.9%)		
2nd or 3rd	81 (58.3%)		69 (50.0%)		0.256
>3rd	9 (6.5%)		7 (5.1%)		
Birth Trauma*	25 (20.7%)		15 (12.8%)		0.120
Maternal Smoking*	45 (37.5%)		37 (31.6%)		0.413
SCBU >2 weeks	15 (11.4%)				
Family environment					
Social Class*					
I	3 (2.5%)		10 (8.0%)		
II	21 (17.2%)		27 (21.6%)		
III (a)	10 (8.2%)		17 (13.6%)		
III (b)	50 (41.0%)		54 (43.2%)		<0.001
IV	23 (18.9%)		14 (11.2%)		
V	15 (12.3%)		3 (2.4%)		
Unemployed Father*	27 (22.3%)		13 (10.2%)		0.010
Single Parent Family*	37 (26.8%)		33 (24.3%)		0.679
Children in Household*	2.8 (1.5)	138	2.4 (0.9)	137	0.012
Atopic disease					
Asthma*	24 (17.6%)		9 (6.8%)		0.009
Eczema*	26 (19.3%)		6 (4.5%)		<0.001

*The variables marked with * were examined in stepwise multiple regression analysis to determine predictors of early childhood growth and prepubertal growth.*

Parental target

Each child's height was compared to those of their parents by calculating target height and target range using the adult height potential method as described in the previous chapter. These variables were then converted to standard deviation (SD) scores using the 1990 UK standards [Freeman et al 1995]. The mean target height SD score and the mean difference between the child and target height SD scores were significantly different between the short and control groups (table 3:1). Although the short children had shorter parents, they were still more likely to fall below target height. No gender differences were found in either group. The parents of short boys and short girls had similar heights and the discrepancies between child and parental heights were also similar *(boys: -1.20, girls: -1.29, p=0.460)*. Figure 3.1 shows the difference between target and child's height SD scores for each child. The zero line represents target height and the dotted lines target range. For the control children, the discrepancies were distributed evenly around target height and, as expected, approximately 95% fell within target range. Most short normal children, regardless of gender, fell below target height.

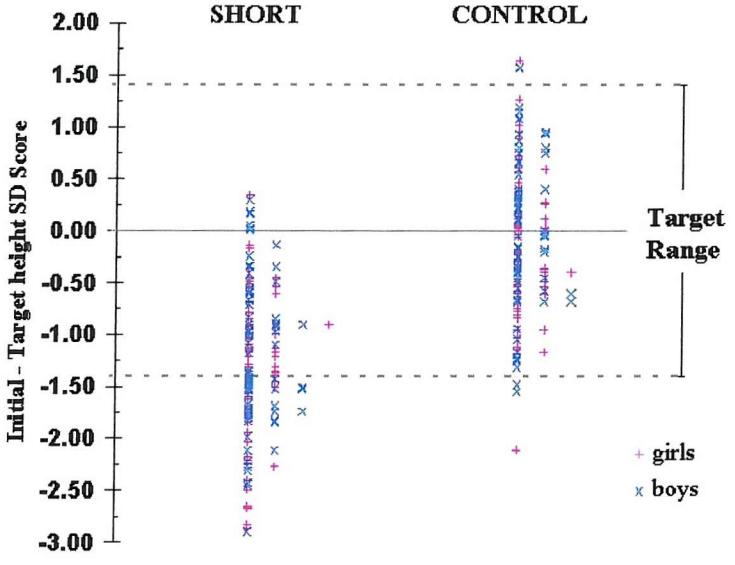


Figure 3.1 *The difference between initial and target height SD score for each child. 57(42%) short but only 3 (2%) control children fell below target range*

Over 100 years ago, Galton [1886] demonstrated what he termed 'regression towards mediocrity in hereditary stature', namely that short parents tend to have short children who are not as short as themselves while tall parents have tall children who are not quite as tall.

More recently, Wright and Cheetham [1999] investigated the heights of approximately 500 children and their parents and confirmed a tendency for offspring to regress towards the mean. They concluded that regression towards the mean was a genetic phenomenon and suggested that instead of using parental target height, the child's height should be compared with the estimated height obtained using the regression equation and parental heights. Regression towards the mean, however, is ***not*** a genetic phenomenon but a statistical concept that occurs for any pair of imperfectly correlated variables [Healy and Goldstein 1978, Bland and Altman 1994a]. Selecting an extreme group based on one of these variables will produce a less extreme mean for the second variable. Consequently, although overall short parents may well produce relatively taller children, short children will be, on average, the offspring of relatively taller parents. The data from the Wessex Growth Study clearly demonstrates this effect. The parents of the short normal children were short, the mean parental height lay on the 8th centile, ***but*** they were not as short as their offspring, whose mean height was close to the 0.4th centile. Indeed, in their investigation Wright and Cheetham also found that the shortest children were short for parents, and using their 'adjusted' height only served to exaggerate this discrepancy. Selective screening for short stature is likely to identify the shortest child in any one family and it is not surprising to find that many have a height below parental target.

Nevertheless, significantly more short than control children were inappropriately short for parents with 57 (42%) short normal compared to only 3 (2%) controls *($p<0.001$)* having a height SDS below target range (figure 3.1) and thus classified as having non-familial short stature (non-FSS). There are, however, two reasons why this may be the case.

First, the calculation of parental target height is based on the assumption that polygenic factors derived from both parents are equal in magnitude, but Ranke [1996] warns that this may not be the case, especially if there are wide differences in height between the parents or if one or both parents are very short. In this study, the mothers and fathers of the short children were both significantly shorter than those of the controls (table 3:1). Interestingly, the mean difference between the heights of spouses was similar in both groups *(SN: 13.7cm, C: 14.6, $p=0.431$)* and close to the mean population difference between men and women. It would appear that assortative mating is equally likely among both groups and that men and women, whether short, average, or tall, prefer to marry someone whose relative height is comparable with their own. Consequently, both parents of the short children were likely to be

short and half the short children had at least one parent whose height was less than the second centile *(SN: 70(51%), C: 7 (5%), p<0.001)*.

Second, target height and target range calculated using the adult height potential method described in the previous chapter is intended for use with the child's predicted ***adult*** height [Tanner 1986b]. Nevertheless, it is commonly used to assess the height of prepubertal children. Indeed, the instructions on the 1990 UK growth charts encourage its use in this way. The correlation between prepubertal height and subsequent adult height is between 0.8-0.9 allowing adult height to be predicted only to within ±9 cm [Tanner 1989]. Ideally, the child's predicted height together with its confidence limits should be plotted on the same growth chart as target height and target range. Height predictions based on solely prepubertal heights do not take in to account the child's tempo of growth, and there is evidence to suggest that short normal children have a slower tempo of growth [Rekers-Mombarg et al 1996]. A better prediction can be obtained by considering the child's tempo of growth [Tanner et al 1983a].

Bone age

A good measure of the tempo of growth is considered to be skeletal maturity [Tanner 1989, Sinclair 1989]. Final adult height is achieved with the fusion of the epiphysis with the diaphysis and skeletal maturity, or bone age, is a measure of this progression. A bone age that is delayed in relation to chronological age indicates a slower tempo of growth and later catch-up growth is assumed [Khamis and Roche 1995]. In the Wessex Growth Study, the bone age of 118 (84%) short normal children was assessed using the RUS-TW2 method [Tanner et al 1983b] shortly after recruitment. Due to ethical considerations, it was not possible to assess the bone age of the control group and so comparisons have been made only with the original standards where, for both sexes, the mean delay is 0 and the standard deviation one year. As shown in figure 3.2, the distribution of bone age SD score was approximately normal, but there was a mean delay of around 8 months with 50 (42%) children having a delay of more than one year. There were no gender differences either for the mean bone age delay *(boys: -0.75, girls: -0.61, p=0.408)* or the number delayed by more than one year *(boys: 25 (39%), girls: 25 (46%), p=0.143)*.

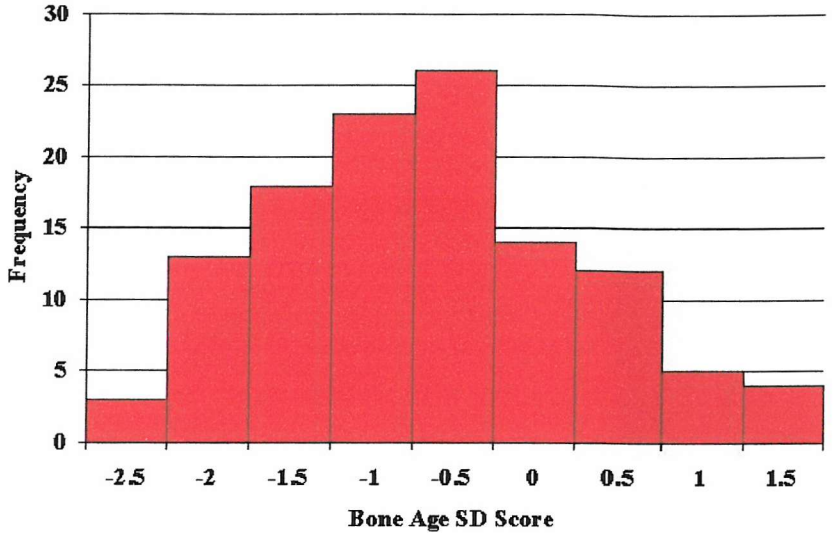


Figure 3.2 *Distribution of bone age SD score for short normal children. The mean (SD) delay was -0.69 (0.97) years*

Predicted height

For those short normal children with a bone assessment, the predicted adult height was calculated using the TW Mark II regression equations formulated by Tanner et al [1983b] according to the method described in Chapter 2. These prediction equations were devised from children that included very short and very tall children and are considered suitable for children of all heights [Tanner et al 1983a]. As expected, the short normal children were predicted to show some catch-up growth with the mean height of the short group calculated to increase from the 0.4^{th} centile to the second centile (table 3:1). Rather surprisingly, in spite of having similar bone age delays and height SD scores, short normal girls were expected to become relatively taller adults than short normal boys. The mean adult height SD score for girls was predicted to be –1.61 compared with –2.59 for boys *($p<0.001$)*. Few studies, however, have examined final height outcome with the height predictions of untreated, short normal children. Those studies that do exist tend to be based on adolescent children diagnosed with CDGP [Crowne et al 1990, Bramswig et al 1990, Sperlich et al 1995, Albanese and Stanhope 1995]. However, a community study of 82 short normal, prepubertal children [Lacey and Parkin 1974b] traced 50 (25 boys) as adults and found that almost all boys were taller than predicted compared with less than half the girls [Parkin 1989].

Birth weight

Birth weight is an indication of prenatal growth and birth size is to some extent predictive of future growth [Goldstein 1971, Rona et al 1978, Bacallao et al 1996]. Indeed, for the control children in this study, a correlation was found between birth weight and height at recruitment *($r=0.27$, $p<0.001$)*. Those who had been heavier at birth tended to be taller children. It was not then surprising to find that the short normal children had been smaller babies. After adjusting for gestational age, their mean birth weight lay on the 10^{th} centile compared to the 55^{th} centile for the controls (table 3:1). All birth weights were reported, but mothers' recall of birth weight has been shown to be accurate [Troy et al 1996, O'Sullivan et al 2000].

3.3 Social and environmental background

Birth History

Birth weight is influenced by both genetic and environmental factors [Carr-Hill et al 1987]. While some reduction in birth weight of the short normal children, the offspring of short parents, might have been expected, 15 (11%) short and no controls had a birth weight that could be considered very low ($<0.4^{th}$ centile or <1500g). Low birth weight is associated with the circumstances surrounding birth such as birth order, prematurity and maternal smoking [Cogswell and Yip 1995], but no significant differences were found between the groups for these variables (table 3:1). Indeed, the birth histories of the two groups were remarkably similar. Most children, short and control, had been born at term and a similar number of mothers in each group smoked during the pregnancy. The mean maternal age was similar for short and control mothers. Slightly fewer children in the short group were first born, but the difference was not significant. Birth trauma, defined as breech or caesarean delivery, multiple birth, or extreme foetal distress was reported for a similar number of short and control children. Nevertheless, a substantial number of short normal children were evidently perceived to have problems at birth as 25 (19%) had been admitted to the neonatal care unit, with 15 (11%) remaining there for more than one week. Comparable data for the control group was unavailable but, according to local norms, these figures were deemed to be approximately twice the expected number. It has been estimated that 66% of the variance of birth weight is due to environmental factors [Robson 1986] and it may be that the social circumstances of short normal children made them appear to be more at risk.

Family structure and social background

There were marked differences in the socio-economic conditions of the short and control groups (table 3:1). Based on the Registrar General's Classification of Occupations, the fathers of short children were more likely to be in semi-skilled and unskilled manual jobs and fewer in professional and managerial occupations. Furthermore, at the time of recruitment approximately 1 in 4 fathers of the short children were reported to be unemployed compared with only 1 in 10 for controls. For both groups, 3 out of 4 children were living with both parents but the short normal children came from larger families. Family size, social class and childhood stature are linked [Tanner 1986a]. Tanner has hypothesised that in poorer families where there are more mouths to feed, children are less likely to obtain the care needed to maximise genetic potential.

There is little evidence in the present study to suggest that nutrition was less than adequate in any family. The mean BMI of the short normal children was lower than that of the controls, but BMI in children is known to be correlated with height [Garn et al 1986] and the disadvantage of using BMI to assess children of different heights, even after standardising for age and sex, has been pointed out [Freeman et al 1995, Mulligan and Voss 1999]. Healthy children are expected to have similar height and weight centiles [Buckler 1994] and these were comparable for most short normal and control children. Adverse social circumstances, however, whether due to emotional or physical abuse or economic deprivation, are likely to threaten normal growth and development [Rona et al 1978] and unemployment is likely to aggravate any hardship faced. Indeed, it has been shown children with unemployed fathers are shorter than those with employed fathers even after correction for social class, family size, birth weight and parental height [Rona and Chinn 1991].

Medical History

Few acute medical problems had occurred in the early years for either group but parents reported more atopic conditions for the short normal children (table 3:1) who were twice as likely as the controls to be asthmatic and four times as likely to have eczema. As atopic conditions are thought to be more prevalent among the more affluent [Graham et al 1967, Williams et al 1994], this finding was somewhat unexpected given the socio-economic status of the short group. However, low socio-economic class is associated with early childhood wheezing [Lewis et al 1995] and the distinction between true asthma and other respiratory

illnesses is not always clear [Rona and Florey 1980]. It may be that at least some of the short children were suffering from recurring respiratory infection.

A link between atopy, skeletal delay and poor growth has been observed [Ferguson 1982], though it remains unclear whether compromised growth is caused by the condition or its treatment [Ninan and Russell 1992, Doull et al 1995]. In community samples, such as this, where there are few measures of disease severity, atopic conditions do not appear to affect height [Power and Manor 1995, McCowen et al 1998]. In the Wessex Growth Study, short children with atopy had similar heights to those without the condition. However, although the differences were not significant, there was a tendency towards greater skeletal delay for those short children reported to be asthmatic *(mean bone age delay 0.95 years)* and those suffering with eczema *(0.90 years)* while the 11 short children reported to have both conditions were the most delayed *(1.08 years)*.

3.4 Prepubertal Growth

Growth is considered to be a sensitive index of a child's well-being and extreme short stature is a good indicator of organic disease [Lacey and Parkin 1974a, Vimpani et al 1981, Voss et al 1992]. Most children, however, do not start off short but become short. Even those with congenital abnormalities such as Turner syndrome or growth hormone deficiency often have heights within the expected range in early childhood. Although height is an indication of past growth, it could take many years for the height of a tall child to become short even if growth were to stop completely. If short stature was the only criterion to warrant investigation, an unacceptable delay in diagnosis and treatment would result [Tanner 1975, Herber and Milner 1986] but as yet, there are no empirical standards defining poor growth.

In the past, height velocity has been used as a secondary screening tool to identify slow growing children [Ahmed et al 1993, Lindsay et al 1994] but the difficulties of using height velocity have now been recognised [Thakrar et al 1994]. The error inherent in measuring height makes velocity calculations unreliable, at least in the short term [Cameron 1986, Voss et al 1991b]. Moreover, normal velocity is conditional on the height of the child [Bailey 1994]. During the prepubertal years, however, growth is steady and predictable and healthy, prepubertal children are expected to stay close to their particular centile lines [Tanner 1963, Hindmarsh and Brook 1989]. Consequently, it has been suggested that a better method to

identify growth failure might be to consider height centile change over time [Mulligan et al 1994].

Between the ages of two and nine years, the correlation between the successive 12-months heights of a child is greater than 0.9 and approaches 1 with increasing age [Bailey 1994]. Prepubertal height is therefore a good predictor of height one year later. New guidelines have now been proposed recommending that pre-school children crossing the equivalent of two centile channels (a change in height SD score of 1.34) and school age children crossing one channel (a change of 0.67) should be referred for specialist opinion [Hall 1996]. These guidelines are not based on scientific evidence but reflect the theoretical expectation that younger children are more likely to cross centile channels. They also assume that the pattern of growth for children of different heights will be similar, but there are two reasons why this may not be the case.

First, there is evidence to suggest that short children tend to regress towards the mean and become relatively taller adults. Follow-up of the 1958 birth cohort in the National Child Development Study found that over two thirds of those whose height had been below the 5^{th} centile at age seven years attained an adult height above this level [Greco et al 1995]. Indeed, more than half were above the 10^{th} centile although, it should be noted that all final heights were self-reported and therefore likely to be overestimated [Rona et al 1978]. Heitmann et al (1994) also reported spontaneous catch-up growth for a cohort of short boys with again two thirds attaining an adult height above the third centile.

Second, human growth is thought to be self-stabilizing or 'target-seeking' [Tanner 1963]. The target is considered to be the genetic structure. Target-seeking is most often demonstrated during the first year of life where the negative correlation between birth size and size at one year indicates a tendency for large babies to catch-down and for small babies to catch-up [Tanner 1994]. The growth of a child can also be pushed off course due to illness, malnutrition or psychological stress but once the restrictive entity has been removed, a period of rapid growth often ensues until growth returns to its natural curve [Prader 1963].

At recruitment, many short normal children were inappropriately short for parents suggesting that they had already been deflected from their natural growth curve and indicating a potential for catch-up growth. The children were healthy with no evidence of undernutrition

but, compared to the controls, they were more likely to suffer economic hardship typically coming from larger families of low socio-economic class and many fathers were unemployed. Such an environment is unlikely to be conducive to optimum growth. Indeed, the majority had some degree of bone age delay and were expected to improve their height centile at some stage. Bone age is thought to be a measure of the *tempo of growth* [Tanner 1989]. Those with a slow tempo are expected to grow more slowly throughout childhood but to have a later pubertal spurt and to continue to grow for longer than those with a more rapid tempo.

To establish whether short normal children were more likely to experience catch-up growth or continue in a downward trajectory, the prepubertal pattern of growth for both short and control children was examined. All children who had been measured for at least two years between the ages of six and nine years were included. Height and height SD scores at these two ages were calculated according to the method described in Chapter 2. The prepubertal change in height SD score (ΔHSDS) was calculated by subtracting the height SD score at nine from that taken three years earlier. The average annual velocity over the three-year period was also calculated. Data was available for 127 (68 boys) short normal and 125 (68 boys) control children. Those excluded from the analysis included 16 (7 controls) who were lost to follow-up, 10 (8 controls) whose first measurement was recorded after the age of seven. Two short boys with severe social deprivation who were adopted shortly after recruitment and showed immediate catch-up growth (figure 3.3) were also excluded from this analysis.

3.5 The pattern of growth

At the age of six, the mean height of the short normal children lay on the 0.4th centile (table 3:2) and there was no significant difference in the height SD score of short boys and girls *(boys: -2.69, girls: -2.69, p=0.986)*. By comparison the mean height of the controls lay on the 42nd centile and control boys were a little taller than control girls *(boys: -0.05, girls: -0.38, p=0.003)*.

At the age of nine, there was little change in the relative height positions of the two groups. The mean heights of short and control children now lay on the 0.6th and 46th centile,

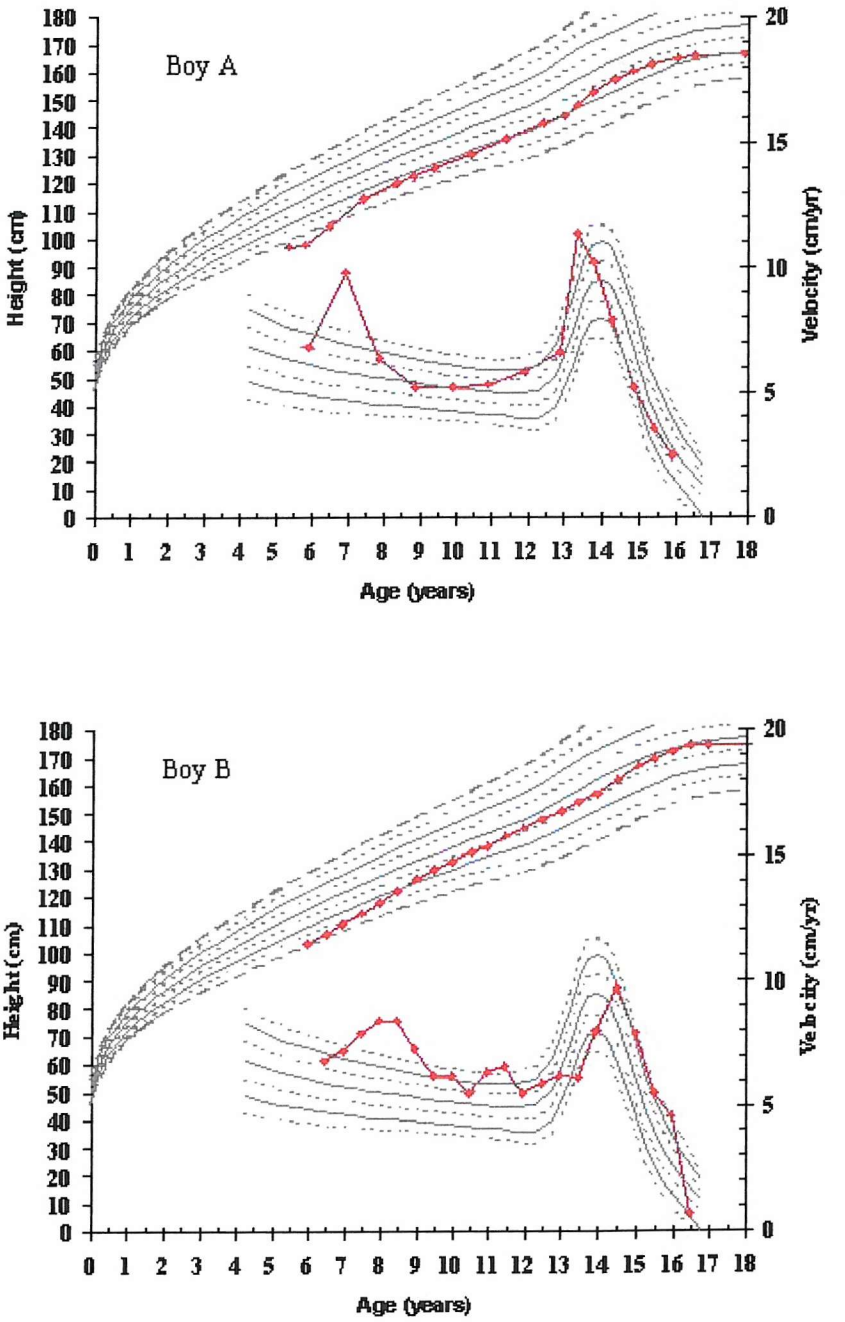


Figure 3.3 *The individual height and height velocity curves of two boys who showed dramatic catch-up growth following adoption*

respectively. The control boys remained slightly taller than the control girls *(boys: +0.05, girls: -0.29, p=0.005)* but again no gender differences were found in the short group *(boys: -2.53, girls: -2.54, p=0.794)*.

Table 3:2: *Summary of prepubertal auxological data for short normal and control children. Results show mean (SD) for each variable*

	Short (n=127)	**Control (n=125)**	**p-value**
Age 6 years			
Height (cm)	102.6 (1.8)	114.7 (3.1)	<0.001
Height centile	0.4th	42nd	
Height SDS	-2.69 (0.36)	-0.20 (0.63)	<0.001
% below target range	41.1%	1.7%	<0.001
Age 9 years			
Height (cm)	118.3 (2.5)	132.5 (4.0)	<0.001
Height centile	0.6th	46th	
Height SDS	-2.53 (0.42)	-0.10 (0.67)	<0.001
% below target centile	33.9%	1.7%	<0.001
Average velocity (cm/yr)	5.25 (0.46)	5.93 (0.51)	<0.001
ΔHSDS	0.16 (0.24)	0.10 (0.24)	0.039

Height gain

In centimetre terms, the short group grew more slowly than the controls. Between the ages of six and nine years, their mean gain in height was 15.7cm compared with 17.8cm for the controls *(p<0.001)*. However, the mean growth of both short normal and control children stayed close to their initial mean height centile lines (figure 3.4). No significant gender differences were found in either group. For the control group, there was a significant correlation between height SD score at age six and height gain over the following three years *(r=0.38, p<0.001)*. Even within the short group, where the range of initial heights was narrower, there was a tendency for those who were taller to grow faster during the prepubertal phase of growth *(r=0.18, p=0.044)*. These data confirm that height velocity is conditional on the height of the child [Bailey 1994], and that children of different heights must be judged by different height velocity standards. Indeed, as a group the mean rate of

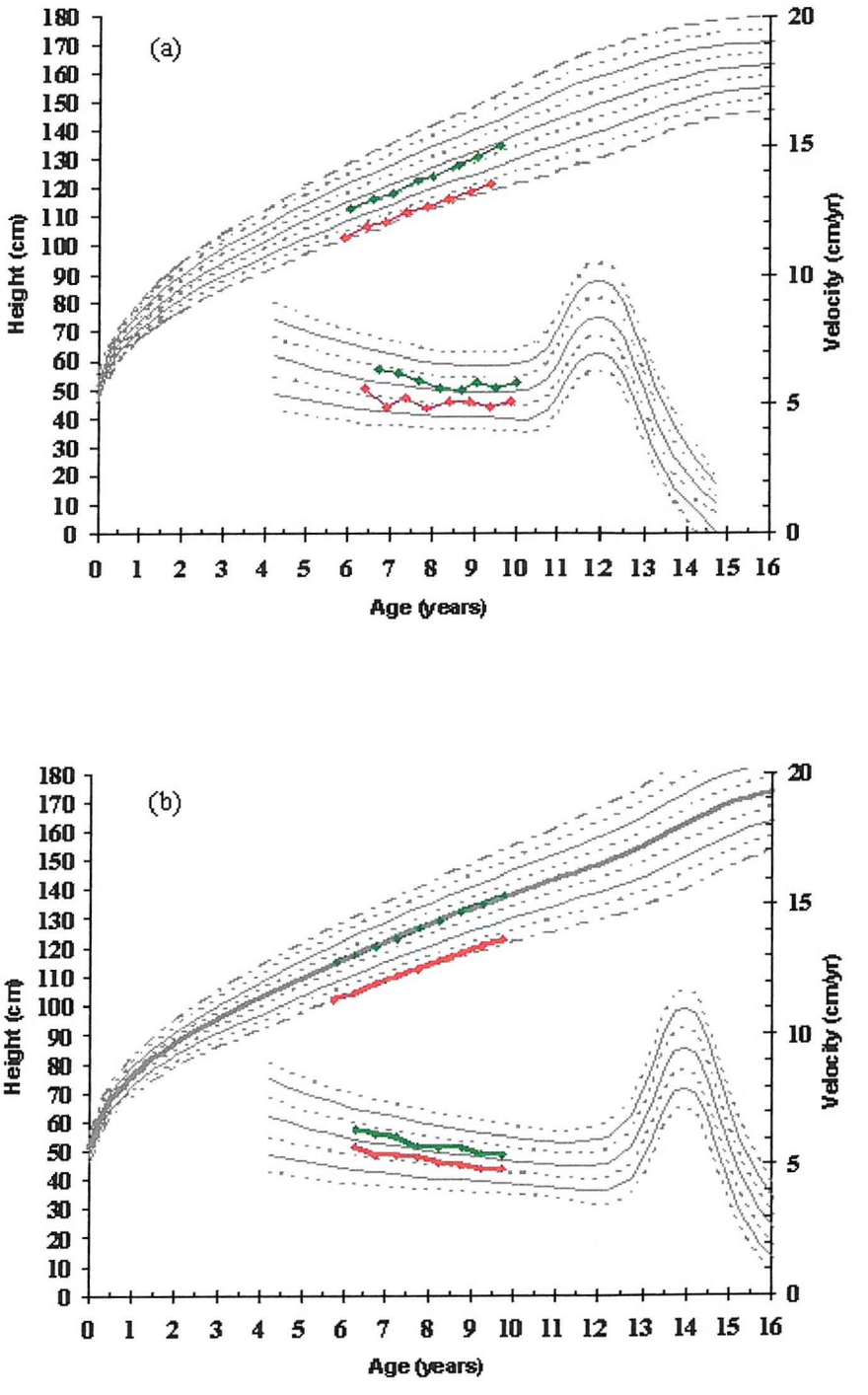


Figure 3.4 *The mean prepubertal growth in height and height velocity of short — and control — children. Girls are shown in (a) and boys (b).*

growth for the short children was close to the 25th centile but nearer the 50th centile for a child of average height (figure 3.4).

Height velocity

Growth velocity is considered to be the key to growth assessment in childhood [Hindmarsh and Brook 1986]. While recognising that the short child whose height remains on the 3rd centile will have a height velocity on the 25th centile compared to the 75th centile for a tall child, these authors make the assumption that the limits of normality for height velocity range between the 25th and 75th centile. However, the error that is inherent in measuring height makes velocity calculations unreliable [Voss et al 1991b], and the height velocity for a short child will inevitably fluctuate around the 25th centile. Indeed, over the prepubertal period of growth, 89% of the short normal and 52% of the controls were observed to have at least one velocity lower than this. In a recent community study, Thakrar et al (1994) confirmed that poor growth identified by a velocity below the 25th centile led to a high number of false positive referrals. It has been suggested the sensitivity would be improved by referral of only those short children with ***two*** successive low velocities as the probability of this is only 0.0625 (0.25 * 0.25) [Brook et al 1986]. This may well be true for the population, but the likelihood of two successive annual velocities below the 25th centile is clearly higher for the short normal child.

Change in height SD score

Although the mean growth of both groups stayed close to their initial mean height centile lines, the height SD score of most children changed to some extent between the ages of six and nine. Figure 3.5 shows the individual change in height SD score for each child. Most children showed only small shifts in height centile and, except for 2 short and 3 control children, height SD score did not alter by more than 0.67, the equivalent of one centile channel on the 1990 UK charts. The change in height SD score was slightly greater for the short group (table 3:2), but a paired t-test analysis revealed a small but significant improvement in height SD score for both groups (*SN: HSDS at 6yr=-2.69, HSDS at 9yr=-2.53, $p<0.001$; C: HSDS at 6yr –0.20, HSDS at 9yr=-0.10, $p<0.001$*).

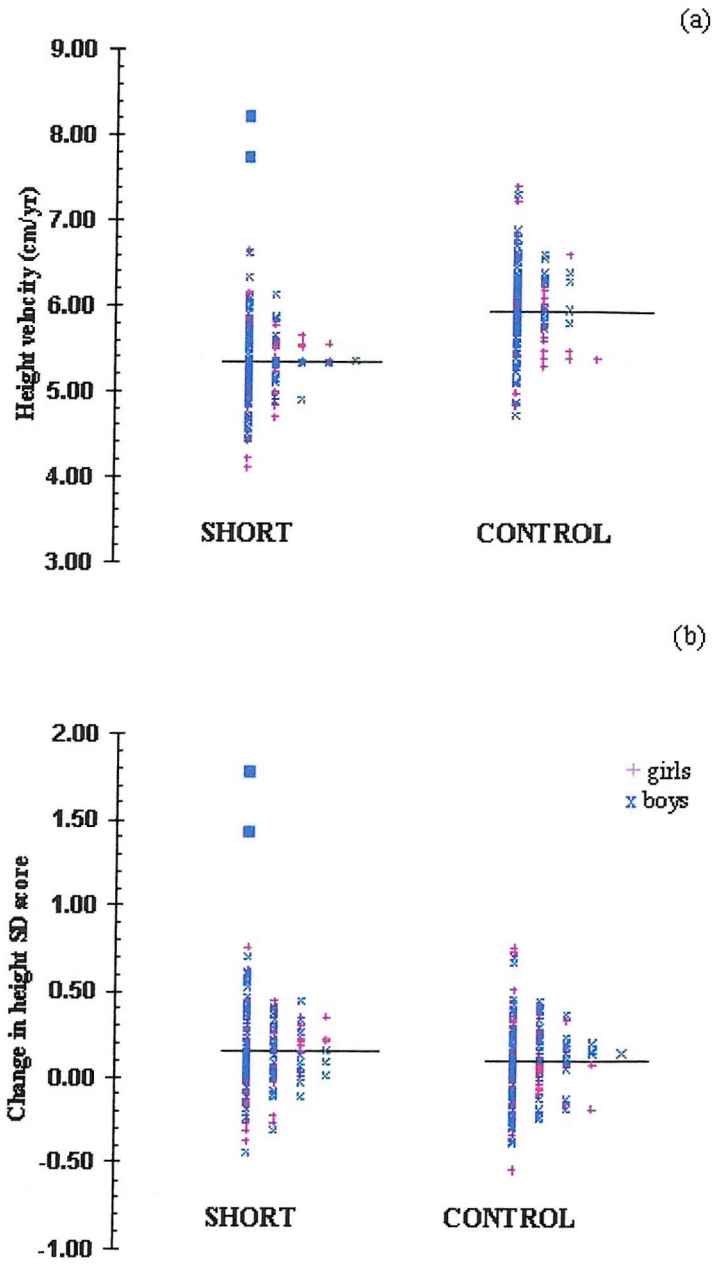


Figure 3.5 *The individual prepubertal growth of short normal and control children between the ages of 6 and 9 years illustrated by (a) the mean annual height velocity and (b) the change in height SD score. The two short children with catch-up growth following adoption are represented by* ■

No gender differences were noted in any group, and no correlation was found between the height SD score at age six and ΔHSDS over the following three-year period (*SN: r=-0.072, p=0.419; C: r=-0.010, p=0.914*).

In absolute terms, the short children grew at a slower rate than their taller controls but there was little difference in the pattern of growth between the short and control groups. Just as many in each group diverged from their original height centile though in most cases, only small shifts were observed. This degree of canalisation is not unexpected given that the correlation between successive annual prepubertal height measurements is greater than 0.9 [Bailey 1994]. The variability in the change in height does increase as the measurement interval increases [Sorva et al 1990, Cole 1997] but, even over a three-year period between the ages of six and nine, the correlation still exceeds 0.9 [Cole 1997]. For the control children in the Wessex Growth Study, the correlation between height SD scores at six years and nine years was 0.933, equivalent to a correlation of 0.966 for the whole population, rather than that truncated at the 10^{th} and 90^{th} centile.

In exceptional circumstances, a sudden change in height centile can occasionally occur, although this usually follows the identification and treatment of pathology or psychosocial deprivation [Tanner 1963]. Indeed, two of the short boys excluded from this analysis are such cases. Shortly after recruitment, both boys were adopted and showed dramatic 'catch-up' growth (figure 3.3). These cases also demonstrate the 'target-seeking' nature of height as discussed by Tanner (1963), who hypothesised that rapid catch-up growth occurred until the target height for a given age is attained, thereafter growth slows to follow the natural growth of the individual. Both boys were equally short at age six but in the case of boy **A** catch-up growth ceased when height reached the 9^{th} centile whereas boy **B**, who had taller parents, was almost on the 50^{th} centile before rapid growth ceased. Many of the short normal children were from deprived backgrounds and a significant number were inappropriately short for parents (table 3:2). It may be that more short normal children have the potential for similar catch-up growth. However, not all children show the same physiological response to an adverse environment [Gilmour and Skuse 1999]. Sexual, emotional, and physical abuse are reported to be far more common in the general population [Skuse and Bentovim 1993] than psychosocial dwarfism [Skuse et al 1996].

Nor is it surprising that, in spite of remaining in a less favourable environment, short children were no more likely than controls to exhibit poor growth. It has already been observed that much of the height discrepancy due to poor social circumstances is established before the age of five and does not alter significantly during the prepubertal phase of growth [Smith et al 1980]. Rona and Chinn (1991) also found that height gain after the age of five was not associated with father's employment status. These data confirm that the critical period for growth occurs before school entry and that children may become less vulnerable to environment effects as they grow older.

Sorva et al (1990) analysed the growth data of over 2000 Finnish children recorded at routine health surveillance and calculated the changes in height SD score during 1, 2 and 5-year periods over the range of 2 to 12 years. They found that, regardless of measuring interval, mean ΔHSDS was close to zero. Variability, however, increased as the measurement interval increased and decreased as age increased reaching its lowest point before the onset of puberty. In their study, the mean (SD) of the ΔHSDS was found to be 0 (0.27) between the ages of seven and nine. These findings were confirmed by Cole (1997) who showed that in the reference population, the mean of the ΔHSDS is zero and the SD of ΔHSDS is $\sqrt{2(1-r)}$ where r is the correlation between height SD scores at age_1 and age_2. Using data collected under research conditions from the French longitudinal growth study, he estimated that the mean (SD) for the ΔHSDS to be 0 (0.22) and 0 (0.30) between the ages of seven and nine and the ages of six and nine, respectively.

Table 3:2 shows the mean (SD) of the ΔHSDS for both the short normal and control children in the Wessex Growth Study between the ages of six and nine. For both groups, the standard deviation of the ΔHSDS was 0.24, comparable to the findings of Sorva and to the estimates of Cole, but the mean change for ***both*** groups was significantly greater than zero. Some regression towards the mean might be expected for very short children though this is hardly likely to reach significance in only a three-year period. Nor can this explain the increase in the control group, whose mean height was only a little below the 50th centile. It is also unlikely that this apparent increase in height centile is the result of a continuing secular change in height as the standards were introduced in 1995 and based on children measured in the 1990s [Freeman et al 1995]. Moreover, these standards have been found to be appropriate for current day school children [Cotterill et al 1996, Rudolf et al 2000]. Indeed, to assess the

impact of recent height monitoring guidelines [Hall 1996], the longitudinal data of 486 children measured by school nurses were examined and compared with measurements from the Wessex Growth Study [Mulligan et al 1998]. School nurses had routinely measured the children in school on two occasions and, as expected, the mean ΔHSDS was close to zero although variability was slightly increased (*mean (SD)= -0.01 (0.35)*). By comparison, the same researcher, using the same equipment had measured the children in the Wessex Growth Study every six months. The most likely explanation may be that research subjects are 'trained' to be 'good' subjects by multiple attendances eliminating some of the error associated with postural change of standing height [Wales and Gibson 1994].

3.6 Factors associated with prepubertal growth

Pre-school growth

No attempt had been made to obtain retrospective height measurements prior to school entry. Nevertheless, height is an indication of earlier growth while parental height is considered to be a measure of genetic potential. Thus, the discrepancy between these two variables is an indication of a child's past health and well-being. Consequently, as a measure of growth prior to recruitment, the difference between target height centile and the child's height centile was calculated for each individual. Table 3:3 shows the correlations between genetic and environmental variables and this discrepancy.

For the short children, several social factors were associated with poor pre-school growth. The children were *more* likely to have a height below target if they came from larger families and were *less* likely to be short for parents if their father was in unskilled manual employment or was unemployed. The association of large family size with poor childhood growth confirmed previous reports [Lacey and Parkin 1974b, Neligan and Prudham 1976, Gulliford et al 1991], but it was rather surprising to find that low social class and unemployment were associated with a smaller discrepancy between child and parent. Nonetheless, Schumacher and Knußman (1979) have observed that in families of low social class, shorter siblings have the least chance of upward mobility. These data possibly reflect another example of the 'recycling of poverty' [Garn et al 1984] with many parents themselves experiencing less than optimum childhood conditions and failing to reach their own genetic potential. It may be that these measures of socio-economic disadvantage are also a reflection of the deprivation suffered by parents.

Table 3:3 *Correlation coefficients of genetic and environmental variables with the discrepancy between child height SD score at recruitment and target height SD score.*

	SHORT			CONTROLS		
	N	**R**	***p-value***	**N**	**R**	***p-value***
Genetic profile						
Initial Body Mass Index	128	0.04	0.618	123	-0.15	*0.093*
Birth weight	130	-0.08	0.345	128	-0.04	*0.637*
Bone Age SDS	114	0.26	0.005*	-	-	-
Birth history						
Maternal age	110	-0.04	0.655	108	-0.00	*0.975*
Low Birth weight (<0.4)	132	0.09	0.284	-	-	-
Premature (≤ 36 weeks)	133	-0.01	0.898	128	0.16	*0.070*
Birth Order	135	0.00	0.986	129	-0.07	*0.432*
Birth Trauma	118	0.07	0.431	112	0.16	*0.084*
Maternal Smoking	118	0.05	0.619	112	0.03	*0.739*
Family environment						
Social class	119	-0.20	0.033*	121	0.02	*0.820*
Unemployed father	118	-0.19	0.040*	125	0.04	*0.629*
Single parent	134	0.02	0.817	127	0.07	*0.412*
Children in Household	136	0.22	0.011*	129	0.16	*0.071*
Atopic disease						
Asthma	132	0.12	0.174	125	0.05	*0.566*
Eczema	131	0.29	0.001*	125	0.25	*0.005**

* *denotes significant correlations.*

Eczema was also associated with a larger discrepancy between child and parents' heights for both short *(with eczema: 1.67 (0.75), without eczema: 1.18 (0.64), p=0.001)* and control *(with eczema: 0.95 (0.25), without eczema: 0.05 (0.70), p=0.005)* children. Several authors have reported that children with atopic dermatitis are more likely to suffer growth impairment [Kristmundsdottir and David 1987, Patel et al 1998], especially when the condition is severe [Masserano et al 1993].

There is, however, also evidence to suggest that atopic conditions are associated with CDGP and that catch-up growth occurs during puberty resulting in a final height within parental expectations [Patel et al 1997]. No comparable data were available for the control group, but it is of interest to note that there was a tendency towards greater skeletal delay for those short children reported to be asthmatic (mean bone age delay 0.95 years) and those suffering from

eczema (0.90 years) while the 11 short children reported to have both conditions were the most delayed (1.08 years).

Those short children with the largest bone age delay were more likely to be short for parents (figure 3.6). Although pathological conditions may well result in skeletal delay, nutrition, genetics and deprivation also play a part [Cole and Cole 1992, Matkovic 1996]. In this study, bone age delay among the short children was significantly correlated with birth weight *(r=-0.29, p=0.002)* and social class *(r=0.22, p=0.025)*. It may well be that skeletal maturation is the best proxy for deprivation as suggested by Cole and Cole (1992).

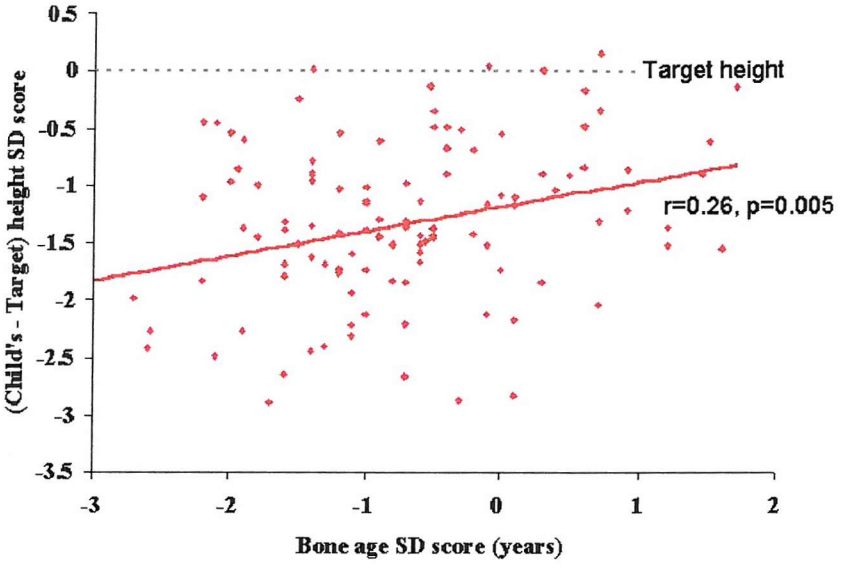


Figure 3.6 *Relation between skeletal maturation and pre-school growth measured by the difference between child and parental target height. Those with the most bone age delay were shorter for parents*

To eliminate confounding variables and determine predictors of poor childhood growth, a step-wise multiple regression analysis was performed examining the biological and environmental variables indicated in table 3:1. The results are shown in table 3:4. For the short normal group, reported eczema and bone age delay were significant predictors and together accounted for 14% of the variance. Eczema was significant for the control group but accounted for only 6% of the variance.

Table 3:4 *Results of a stepwise regression analysis to find predictors of childhood growth as measured by the discrepancy between the child's height and target height*

Step	Variable	R^2	Change in R^2	F-ratio	*p-value*
Short children					
1	Eczema	0.084		8.61	*0.004*
2	Bone age delay	0.135	0.049	7.723	*0.001*
Control children					
1	Eczema	0.061		6.60	*0.012*

Prepubertal growth

As height velocity was found to be dependent on the initial height, prepubertal growth was defined as the change in height SD score (ΔHSDS) between the ages of 6 and 9 years. Table 3:5 shows the correlation between genetic and environmental variables and ΔHSDS. Few variables accounted for even 1% of the variance in prepubertal growth as measured by ΔHSDS. No variable was significantly correlated for the control group but among the short normal children there was a slight tendency for lighter babies to gain the most height. This may well be a chance finding arising from multiple testing.

In a stepwise multiple regression analysis, none of the variables indicated in table 3:1 was able to predict ΔHSDS for either group. Although short stature and poor growth prior to school entry were clearly associated with several biological and environmental factors, none were identified that could predict those who would grow well, or indeed badly, during the prepubertal phase of growth. A few children, 2 (1 boy) short and 3 (1 boy) control, have grown well and improved their height centile by as much as one centile band width but as a group, neither short nor control children have shown any perceptible change in height SD score. At recruitment, many of the short normal group were considered to be inappropriately short for parents (figure 3.1) and in this respect, no significant improvement was observed before puberty (table 3:2).

Table 3:5 *Correlation coefficients of genetic and environmental variables with the prepubertal change in height SD score*

	SHORT			CONTROLS		
	N	r	*p-value*	N	r	*p-value*
Genetic profile						
Initial height	127	-0.14	0.126	125	-0.00	*0.964*
Initial Body Mass Index	121	-0.04	0.632	118	-0.02	*0.876*
Birth weight	123	-0.18	0.048*	123	0.00	*0.997*
Target Height	124	0.03	0.745	117	0.16	*0.077*
Child SDS-Target SDS	124	-0.09	0.304	116	-0.14	*0.130*
Bone Age SDS	106	-0.21	0.831	-	-	-
Birth history						
Low Birth weight (<0.4)	125	0.16	0.079	-	-	-
Premature (≤ 36 weeks)	126	-0.08	0.378	123	0.02	*0.863*
Birth Order	127	0.15	0.086	124	0.05	*0.598*
Birth Trauma	116	0.15	0.108	112	-0.03	*0.777*
Maternal Smoking	115	0.00	0.996	112	0.09	*0.338*
Family environment						
Social class	110	-0.02	0.810	114	-0.17	*0.075*
Unemployed Father	110	-0.01	0.914	115	0.02	*0.847*
Nuclear Family	126	0.08	0.384	122	0.06	*0.486*
Children in Household	126	0.11	0.230	124	-0.10	*0.286*
Atopic disease						
Asthma	124	-0.01	0.908	119	-0.11	*0.246*
Eczema	123	-0.03	0.711	119	-0.16	*0.076*

** denotes significant correlations.*

Skeletal maturation does not appear to predict either the *'tempo'* of growth or *'catch-up'* growth before puberty. These data show that those with bone age delay were no more likely to have a slower growth rate than those with no delay, nor were they more likely to improve their height centile. Consequently, the prognosis for final height may well be poor for those with no delay, though more promising for those with some delay. Provided there has been no undue advancement in skeletal maturity, these short children seem likely to have a delayed pubertal spurt allowing catch-up to occur in adolescence.

3.7 Summary

At school entry, the typical short child has a relatively low birth weight, short parents and a delayed bone age. According to parental report, a substantial number suffered from atopic disease. They are also more likely to come from larger families of low socio-economic class and have an unemployed father. Although many appeared to be inappropriately short for parents, especially those reported to have eczema, most were predicted to have an adult height within the expected range. The most disadvantaged children, as measured by father's occupational status, were *least* likely to be unexpectedly short. Parental height, however, may not be a useful marker of genetic potential as the childhood deprivation suffered by parents may well be masking this potential in succeeding generations.

During the prepubertal phase of growth, the short children did grow more slowly than the controls. The normal rate of height velocity for a short child is close to the 25th centile, but it is nearer the 50th centile for a child of average stature. However, in relative terms, the short children grew just as well as the controls. During the early school years, the mean growth of both groups stayed close to their initial mean height centile lines. Some did grow more poorly than others but no variables, genetic or environmental, were found that could predict prepubertal growth. As yet, no discernible catch-up growth has occurred for the short group, and, at the age of nine, many short normal children remained inappropriately short for parents. However, it may be that the bone age delay observed in the short normal group at recruitment will result in a later pubertal spurt and an improvement in final height centile.

Chapter 4: PUBERTAL GROWTH

The tempo of growth is seen more clearly in the pubertal years. Puberty occurs earlier in girls than in boys but even within the sexes, different children experience puberty at very different ages. Short stature is associated with delayed pubertal development as and many short normal children, especially boys, are referred for specialist opinion in the adolescent years. It is also evident that individual children do not follow a particular centile line during this period. Indeed, the adult heights of children with the same prepubertal heights can differ by as much as 15 cm. The timing, magnitude and duration of the pubertal spurt all contribute towards the adolescent height gain. This chapter will compare the pubertal growth of short and control groups and examine the effect of genetic and environmental variables on the adolescent spurt.

4.1 Introduction

Growth during puberty contributes significantly to final height but the variability in pubertal growth is considerable [Tanner 1962]. Longitudinal studies consistently attribute as much as 30cm or as little as 10cm of final adult height to pubertal growth [Tanner et al 1976, Largo et al 1978, Buckler 1990]. Clearly, the consequences of poor growth during this phase are more critical for those who are already short. The continuing secular trend in the growth of British children has resulted in the publication of new reference curves for height and weight [Freeman et al 1995]. Pubertal growth, however, is still assessed using the 1966 standards of Tanner-Whitehouse [Tanner et al 1966a, 1966b], which may no longer be appropriate, particularly for the short normal child. Many studies have observed that delayed pubertal development is more likely for those who are very short [Ranke and Aronson 1989, Price 1996]. Indeed, a retrospective analysis of the longitudinal growth of over 229 children (145 boys) diagnosed with idiopathic short stature found that the onset of puberty occurred, on average, 1 year later than expected [Rekers-Mombarg et al 1997]. For these children, the longer period of childhood growth resulted in a relative increase in final height.

Nevertheless, the timing of puberty is not in itself predictive of final adult stature. Pubertal height gain depends on the magnitude and the duration of the spurt. A decrease in the magnitude or a shorter duration will negate any height gained as a result of a longer period of childhood growth. It is well documented that the age at peak height velocity (PHV) and the

magnitude of PHV are negatively correlated such that the earlier the peak, the greater the magnitude [Deming 1957, Tanner et al 1966a, Billewicz et al 1981, Tanaka et al 1988, Vizmanos et al 2001]. It is less certain, however, whether the intensity of early pubertal growth fully compensates for the shortened period of growth. Several authors have reported no difference in the final height of early, average and late maturers [Lindgren 1978, Hulanicka and Kotlarz 1983, Abbassi 1998, Vizmanos et al 2001] but others have found that late maturation results in a taller final height [Hagg and Taranger 1991, Liu et al 2000], especially when results are adjusted for prepubertal height [Tanaka et al 1988].

Puberty is one episode in the continuum of growth and to some extent is influenced by previous growth. For example, the rate of prepubertal growth is significantly lower for those with a late adolescent growth spurt [Hagg and Taranger 1992]. Several authors have also observed that early maturers are, on average, taller and heavier throughout childhood than those with pubertal delay [Hagg and Taranger 1991]. An interaction is also evident between birth weight, puberty and the growing process. Binkin et al (1988) found that infants with higher birth weights were likely to remain taller and heavier during infancy and early childhood. This finding has been confirmed by others, who have also noted that the effect of birth weight on body size continues at least until the age of 14 years and, at this age, those who were heavier at birth were also more sexually mature [Mills et al 1986, Bacallao et al 1996]. This relation between birth weight, childhood growth, and pubertal development may reflect nutritional status or, alternatively, an inherited gene complex that predisposes the growth process as a whole to go more quickly and more intensely in some individuals.

Nutrition is undoubtedly an important factor in pubertal development. Indeed, the trend towards taller stature and earlier maturation seen in Western countries over the past 50 years has been attributed to improved health and nutritional status [Delemarre-van de Waal 1993]. There is also evidence that under- and over-nutrition can alter the natural progression of growth. One example of this is low birth weight, especially in conjunction with intrauterine growth retardation (IUGR), which results in poor childhood growth and an earlier than expected, rapidly progressing, puberty [Persson et al 1999, Peralta-Carcelen et al 2000, Ford et al 2000, Ibanez et al 2000]. An earlier onset of puberty is also apparent in obese children [De Simone et al 1995], and in those adopted from developing countries [Virdis et al 1998, Tuvemo and Proos 1993], although in these instances over-nutrition is also associated with above average childhood growth.

It has been suggested that variations in the tempo of growth throughout childhood simply represent the unfolding of a complex mixture of genetic variables [Palmert and Boepple 2001]. As discussed in Chapter 1, pubertal growth does have a strong genetic component. Twin studies consistently reveal greater concordance between monozygotic than dizygotic twins in skeletal maturation, the timing of the adolescent spurt, the age at menarche and Tanner's pubertal staging [Wislon 1986b, Hauspie et al 1994, Loesch et al 1995, Kaprio et al 1995, Beunen 2000 et al]. These studies and others [Koziel 2001] suggest that between 50% and 80% of the variance in the timing of puberty may be genetically controlled.

Nevertheless, environmental factors, reviewed in Chapter 1, are also apparent. Family factors, such as low social class, large family size and low birth order are associated with later pubertal development [Tanner 1962, Billewicz et al 1981, Hulanicka and Kotlarz 1983, Ulijaszek et al 1991, Roberts 1992]. Such home conditions may be a measure of the economic status of the family, but Tanner (1962) has postulated that they are more likely to reflect '*the intelligence and personality of the parents*', and to distinguish '*a good home from a bad one*'. Indeed, psychological stress has been found to adversely affect childhood growth [Blizzard and Bulatovic 1992, Hoey 1993, Montgomery et al 1997]. Recent reports also suggest that stressful life events may modify pubertal progression though the effect seems to be gender dependent: family conflict results in earlier menarche in girls [Graber et al 1995, Kim and Smith 1998, Hulanicka et al 2001], but delayed pubertal development in boys [Malo and Tremblay 1997].

Environmental factors are also thought to be responsible for the population increase in childhood atopic conditions, especially asthma and eczema [Anderson et al 1994], which in turn leads to a delay in skeletal maturation and a delayed entry into puberty [Hindmarsh et al 1993, Patel et al 1998].

The previous chapter showed that as a group, the short normal children in the Wessex Growth Study had a lower mean birth weight than their average height controls, grew more slowly during the prepubertal phase of growth, and were more likely to suffer from atopic conditions. Bone age at recruitment was also delayed and no discernible catch-up growth had occurred before puberty. These data suggest that later pubertal development might be expected for the short normal group. On the other hand, the short normal children were more

likely to experience social adversity, and the low birth weight of many short normal children coupled with non-FSS is suggestive of IUGR. Both these factors are associated with early puberty. This chapter seeks to examine the interaction of genetic and environmental variables on the timing, magnitude, and duration of puberty. The impact of pubertal growth on final height will be explored in the next chapter.

4.2 Subjects and methods

As described in Chapter 2, 107 (60 boys) short normal (SN) and 119 (64 boys) control (C) children were included in the analysis of pubertal growth. The 33 short normal children excluded from the analysis, consisted of 20 children who had been recruited to a trial of growth hormone therapy and received treatment [Walker et al 1990], and 13 lost to follow-up. As this loss represented almost one third of the sample, the remaining short normal children were compared with these 33 children to ensure that the sample was still representative of the typical short normal child. Results are shown in table 4:1.

Table 4:1 *Comparison of the 107 short normal children continuing in the study with the 33 short normal children who were lost to follow-up.*

	REMAINING			EXCLUDED			
	Mean	**SD**	**N**	**Mean**	**SD**	**N**	***p-value***
Initial height SDS	-2.68	0.33	107	-2.86	0.39	33	*0.011*
Bone age SDS	-0.69	0.95	87	-0.68	1.02	31	*0.972*
Predicted height SDS	-2.11	0.61	87	-2.25	0.63	31	*0.295*
Birth weight SDS	-0.87	1.17	103	-1.00	1.21	31	*0.590*
Target height SDS	-1.45	0.66	104	-1.65	0.64	31	*0.141*
(Target – Initial) height SDS	1.24	0.72	104	1.24	0.70	31	*0.985*
Gender							
male			60 (56%)			16 (49%)	*0.594*
female			47 (44%)			17 (51%)	
Social Class							
I & II			19 (21%)			5 (16%)	
III(a)			8 (9%)			2 (6%)	
III(b)			35 (39%)			15 (47%)	*0.570*
IV			15 (17%)			8 (25%)	
V			13 (14%)			2 (6%)	

Those excluded from the analysis were slightly shorter at recruitment. However, although the difference was statistically significant it was not considered to be clinically significant. The

mean recruitment height of both groups was less than the 0.4^{th} centile and the range of heights was similar. No other significant differences were found.

Five of the SN boys included in this analysis had been referred for specialist opinion in late adolescence and were prescribed a short course of low dose oxandrolone treatment. In all cases, treatment commenced after the age of 14 years. Such treatment does result in growth acceleration but several studies have shown no effect on the pattern of sexual maturation, pubertal growth or final adult height [Joss 1989 et al, Bassi et al 1993, Tse et al 1990]. Consequently, these boys were not excluded from this analysis.

Boys and girls were analysed separately to allow for the substantial gender differences in pubertal development. The methodology used to examine the adolescent growth spurt is described fully in Chapter 2 and summarised below.

Height, weight and BMI at the age of eight years were taken as the pre-puberty baseline data. Annual velocities were calculated and used to estimate the magnitude and age of peak height velocity (PHV). The mean pubertal growth spurt for each group was found by centring individual height velocity curves on age at PHV, as described by Tanner et al (1966a). The mean age, height velocity and weight velocity at each measuring point before and after PHV were then calculated. Age at menarche for each girl was recorded to the nearest month.

Target height and target range were calculated as described in Chapter 2 and converted to SDS using the standards of Freeman et al (1995).

Parents were interviewed when the children were between 12 and 14.5 years (mean age 13.5 years) and provided further information on the child's medical and social history. In particular, the presence and treatment of atopic disease were recorded: atopy and its treatment are associated with the timing of puberty and at recruitment, more short than control children were reported to suffer from asthma and eczema (table 3:1). Social class was updated based on the occupational status of the chief income earner in the household at that time, according to the Market Research Society (1991).

A TW2 bone age assessment [Tanner et al 1983] made around the time of recruitment (mean chronological age 5.74 yr) was available for 38 (81%) and 49 (82%) of the short girls and short boys, respectively.

4.3 The pubertal growth of girls

4.3.1 Genetic, environmental and health profile

A comparison between short and control groups of the genetic, environmental and health variables reported by parents when the girls were between 12 and 14.5 years is shown in table 4:2.

Most girls were born at term and a similar number of mothers in each group smoked during the pregnancy. However, fewer of the short girls were first born and their mean birth weight was less than that of the controls.

The parents of the short girls were shorter than those of the controls. Even so, at entry to the study, more short than control girls were inappropriately short for parents. Seventeen (37%) short compared to one (2%) control girl ($p<0.001$) had a height SDS below their target range and so could be classified as having non-familial short stature (non-FSS).

Social class distribution was similar for both groups.

No significant differences were found between the numbers of short and control girls reported to have atopic disease (asthma, eczema, hay fever or allergies) with 15 (33%) short and 24 (44%) control girls having at least one condition ($p=0.305$). In addition, atopic conditions requiring steroid treatment were just as likely for both groups (table 4:2).

At recruitment, the mean height of the short girls lay on the 0.4th centile *(-2.68 ±0.29 SDS)* and all had heights below the 2nd centile according to the 1990 UK data. By comparison, the mean height of the control girls lay on the 34th centile *(-0.40 ±0.52 SDS)* and ranged from the 10th to 70th centile. For both groups, the mean weight centile was similar to the mean height centile (*SN=1st centile, C=30th centile*). The pre-puberty baseline data, recorded when the girls were aged eight years, are shown in table 4:2. During the prepubertal phase of growth,

Table 4:2 *Genetic, environmental and health profile of short and control girls.*

	SHORT GIRLS			CONTROL GIRLS			
	Mean	**SD**	**N**	**Mean**	**SD**	**N**	***p-value***
Birth details							
Birth weight (gm)	2958	621	47	3136	457	54	*0.101*
Birth weight SD*	-0.78	1.30	47	-0.15	1.07	54	*0.010*
Gestation							
Full term >36wks			44 (94%)			47 (87%)	*0.335*
Premature <=36wks			3 (6%)			7 (13%)	
Birth order*							
First born			12 (26%)			29 (54%)	*0.008*
Other			34 (74%)			25 (46%)	
Mothers Smoking*							
Yes			17 (39%)			20 (37%)	*1.000*
No			27 (61%)			34 (63%)	
Parental height							
Target height (cm)	155.4	4.2	46	162.4	4.2	52	*<0.001*
Target height SD	-1.39	0.70	46	-0.24	0.69	52	*<0.001*
Target – Initial Ht SD	1.29	0.75	46	0.17	0.68	52	*<0.001*
Social Class*							
A & B			8 (18%)			11 (20%)	*0.381*
C_1			5 (11%)			12 (22%)	
C_2			13 (29%)			15 (28%)	
D			13 (29%)			8 (15%)	
E			6 (13%)			8 (15%)	
Reported atopic disease (mean age 13.5 years)							
Eczema							
Yes			9 (20%)			5 (9%)	*0.154*
No			36 (80%)			49 (91%)	
Asthma							
Yes			6 (13%)			7 (13%)	*1.000*
No			39 (87%)			47 (87%)	
Hay fever							
Yes			7 (16%)			14 (26%)	*0.229*
No			38 (84%)			40 (74%)	
Allergies							
Yes			2 (4%)			8 (15%)	*0.106*
No			43 (96%)			47 (87%)	
Atopy * (1 or more condition)			15 (33%)			24 (44%)	*0.305*
Steroid Treatment*			8 (17%)			9 (16%)	*1.000*
Inhaled			3			5	
Topical			3			3	
Both			2			1	
Pre-puberty height & weight (aged 8 years)							
Pre-puberty height SDS*	-2.55	0.32	47	-0.33	0.60	55	*<0.001*
Pre-puberty weight SDS	-2.09	0.84	47	-0.25	0.91	54	*<0.001*
Pre-puberty BMI SDS*	-0.65	0.94	47	-0.13	1.02	54	*0.008*

*The variables marked with * were examined in stepwise multiple regression analysis to determine predictors of age and magnitude of PHV and age of menarche. For the short group, bone age at recruitment was also considered.*

some individual divergence occurred but at this age, the height of only one short girl was above the 2nd centile.

Compared with Tanner's standards (mean delay ±SD = 0±1.0 years) [Tanner et al 1983b], the initial mean bone age delay of the short girls was 0.66 ±1.06 years and 17 (46%) were delayed by more than one year.

4.3.2 The mean pubertal spurt

Figure 4.1 shows the mean pubertal growth spurt adjusted for age of PHV of short and control girls plotted against Tanner's standards. Before puberty, the short girls grew more slowly than the controls but the timing, magnitude and duration of the mean pubertal spurt were similar for both groups and near Tanner's 50th centile. No significant differences were found for any pubertal parameter (table 4:3a).

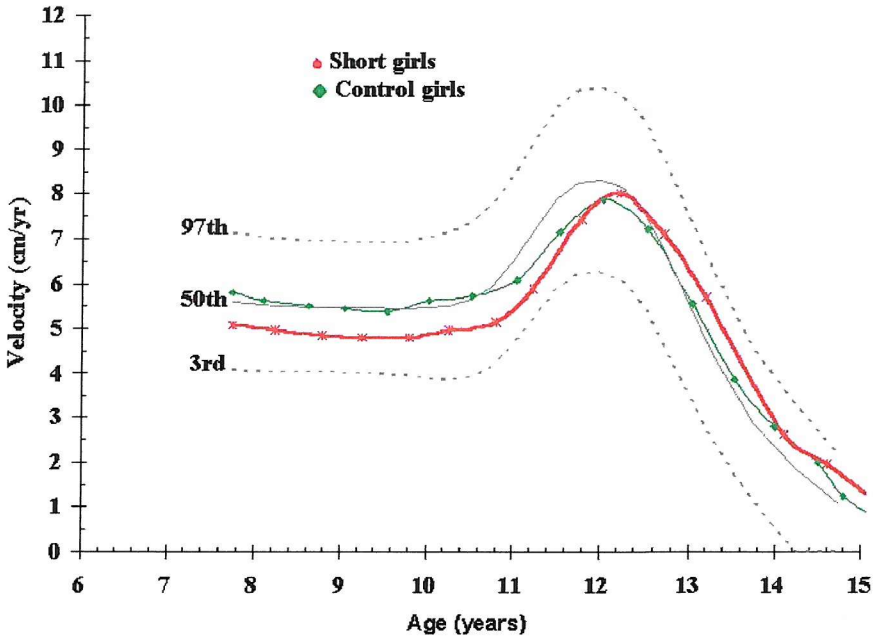


Figure 4.1 *Height velocity, adjusted for age at PHV, of short and control girls plotted against Tanner's standards*

The onset of the pubertal spurt occurred, on average, at a similar age for short and control girls. Until the age of 10.5 years, the mean height velocity of the short girls at each measurement point was less than that of the controls (p-values ranging from <0.001 to 0.027)

but no significant differences were found thereafter. The mean age at PHV, the magnitude of PHV and age at menarche were similar for short and control girls and, for both groups, comparable to the 50th centile values of Tanner et al (1966a, 1966b). The mean height velocity fell below 3cm/yr at a mean age of 14.42 years for the short girls compared to 14.21 years for the controls (*p=0.249*). Puberty lasted for an average of 4.44 years for the short girls and 4.65 years for the controls (*p=0.227*). During the pubertal spurt, the mean height gain for the short girls was 26.4cm compared to 25.7cm for the control girls (*p=0.507*).

Table 4:3 *Characteristics of the pubertal spurt of a) short normal and control girls, and b) short normal and control boys*

	SHORT		**CONTROL**			**Tanner et al**
	Mean (SD)	**N**	**Mean (SD)**	**N**	***p-value***	**(1966a, b)**
a) GIRLS						
Age at Take-off (years)	9.76 (1.07)	43	9.74 (1.26)	53	*0.922*	
Age at PHV (years)	12.25 (0.94)	43	12.04 (1.00)	53	*0.296*	12.0 (0.9)
Magnitude of PHV (cm/yr)	8.09 (0.87)	43	8.00 (1.11)	53	*0.689*	8.33 (0.9)
Age at Completion (years)	14.42 (0.92)	43	14.21 (0.86)	52	*0.249*	
Age at Menarche (years)	13.50 (1.09)	47	13.15 (1.10)	55	*0.112*	13.0 (1.0)
b) BOYS						
Age at Take-off (years)	11.73 (1.19)	60	11.12 (1.01)	64	*0.009*	
Age at PHV (years)	14.47 (0.97)	60	13.80 (1.25)	64	*0.001*	14.0 (0.9)
Magnitude of PHV (cm/yr)	9.61 (1.30)	60	10.06 (1.28)	64	*0.052*	9.46 (1.1)
Age at Completion (years)	16.68 (0.94)	56	16.13 (1.01)	63	*0.001*	

The pattern of weight gain during the pubertal spurt was also similar for both groups (figure 4.2). Short girls gained less weight in the prepubertal years, but during the pubertal height spurt both groups had similar weight gains, which approximated Tanner's 50th centile. The mean gain in weight for the short girls was 20.8kg and 22.1kg for the control girls (*p=0.300*). Between the age of 9 and 10 years, both groups displayed a 'mini-spurt' in weight gain approximately 12 to 18 months before the start of the pubertal height spurt.

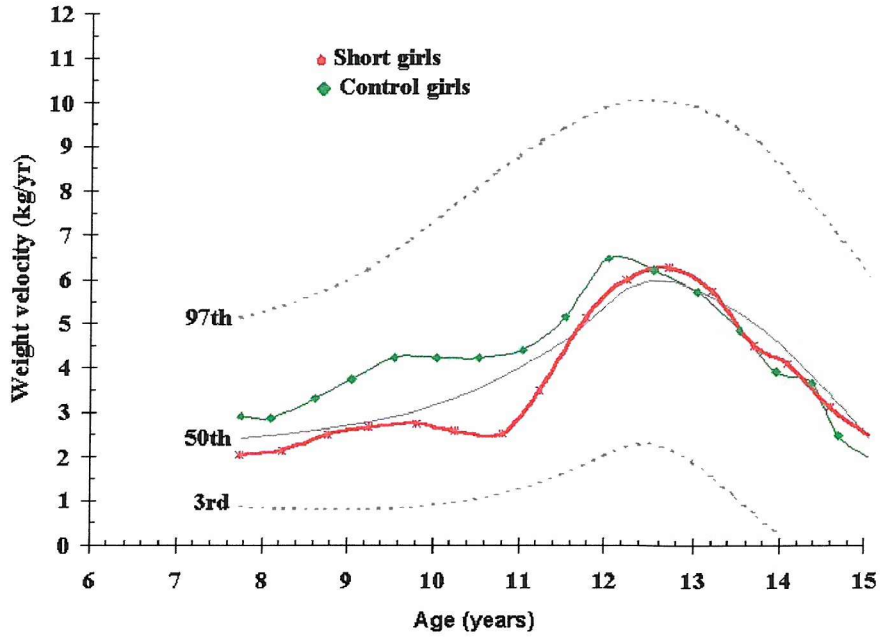


Figure 4.2 *Weight velocity, adjusted for age at PHV, of short and control girls plotted against Tanner's standards*

4.3.3 Individual Variation

Figures 4.3, 4.4 and 4.5 show the individual variation in age at PHV, magnitude of PHV and age at menarche.

Peak height velocity

The distribution of age at PHV was similar for both groups and covered the range 11 years to 13 years for 29 (67%) short girls and 36 (68%) control girls. Five girls (1 SN, 4 C) experienced a delay of more than two years and PHV occurred before the age of 10 years for two girls (1 SN, 1 C).

For most girls, the magnitude of PHV fell within Tanner's 3rd to 97th centile norms. Only one control girl had a PHV above the 97th centile and 3 control girls had a PHV below the 3rd centile.

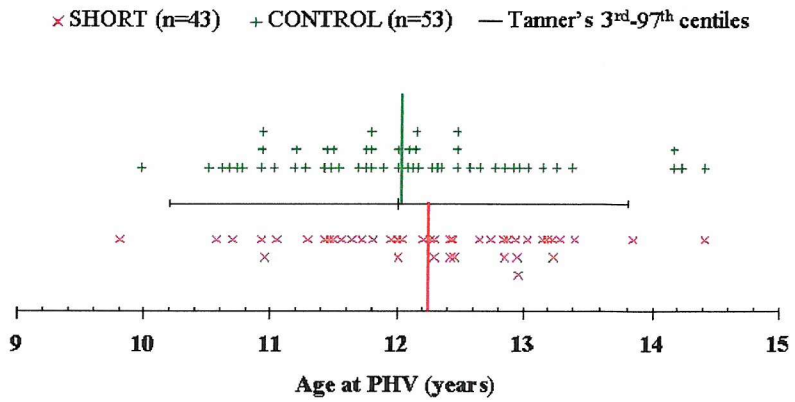


Figure 4.3 *The age at peak height velocity for each short and control girl plotted against Tanner's standards*

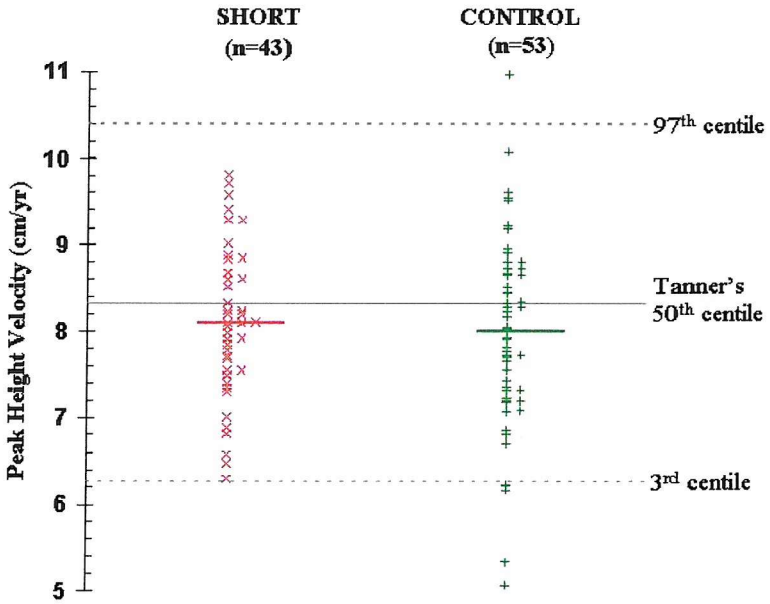


Figure 4.4 *The magnitude of peak height velocity for each short and control girl plotted against Tanner's standards*

Menarche

With the exception of one control girl, menarche was reported to occur after PHV and occurred between the ages of 12 to 14 years for 32 (70%) short and 38 (69%) control girls. Two girls (1 SN, 1 C) reported menarche to have occurred before the age of 11 years and six (3 SN, 3 C) after the age of 15 years. The correlation between age of PHV and age of menarche was similar for short (*r=0.84*) and control (*r=0.89*) girls. The mean interval between PHV and menarche was 1.27 ±0.58 years for short girls and 1.12 ±0.50 years for controls (*p=0.178*).

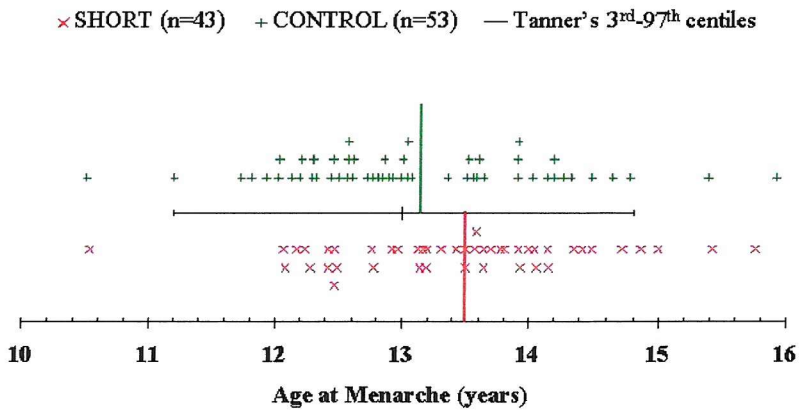


Figure 4.5 *The age at menarche of each short and control girl plotted against Tanner's standards*

Duration and height gain

In this study, the duration of puberty, defined as the period from age at takeoff, through PHV until the annual increment in height was less than 3cm, was also subject to wide individual variation (figure 4.6). There was no difference between the groups and overall the mean duration (SD) was approximately 4.5 (1) years. The pubertal spurt lasted less than 2.5 years for only 2 control girls and more than 6.5 years for 1 control girl.

Height gained during the adolescent spurt ranged from 15.0cm to 36.0cm for the short girls and from 10.8cm to 39.7cm for the controls

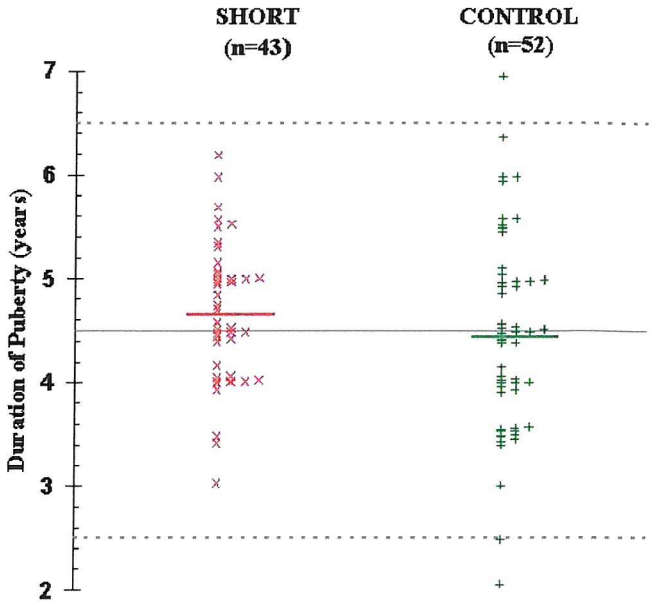


Figure 4.6 *Individual variation in the duration of puberty for short and control girls*

4.4 Factors influencing pubertal growth of girls

The genetic and environmental variables indicated in table 4:2 were examined in a stepwise multiple regression analysis to determine their influence on pubertal development. A summary of the predictors of the timing, magnitude and duration of the spurt are shown in table 4:4a.

4.4.1 Age at PHV

For control girls only, there was a modest but significant negative correlation between age at PHV and pre-puberty height (r=-0.29, p=0.037) indicating a tendency for taller girls to have earlier puberty. The presence of atopy had little effect on the mean age at PHV except when data for short and control groups were combined. In this case, age at PHV was significantly later if the condition was severe enough to warrant treatment with inhaled and/or topical steroids (*steriods=12.61yr, no steriods=12.03yr, p=0.025*).

In a stepwise regression analysis none of the variables tested (table 4:2) was found to predict the age of PHV for short girls but pre-puberty height was entered for the controls (ß=-0.49,

p=0.037). However, for short and control girls together, height was not entered and the only predictor of age at PHV was the presence or absence of steroid treatment, which accounted for 5% of the variance.

4.4.2 Magnitude of PHV

Figure 4.7 shows the relation between age and magnitude of PHV for short and control girls. For control girls the correlation (*r=-0.52*) and hence regression (*β=-0.57*) of PHV on age of occurrence were highly significant and similar to Tanner's values of r=-0.39, β=-0.47. Those with earlier peaks had higher PHV. However, in spite of having similar means and variances for both age and magnitude of PHV, no significant relationship was found for the short girls. No other variable was found to correlate with or predict the magnitude of PHV for either group or for both groups combined.

4.4.3 Age at menarche

For both groups, age of menarche correlated with pre-puberty BMI (*SN: r=-0.38, p=0.011; C: r=-0.41, p=0.002*). Thinner girls tended to have a later menarche. As with age at PHV, the presence of atopic disease had a significant effect on age of menarche only when data for both groups were combined and the condition required treatment with inhaled and/or topical steroids. Those treated with steroids tended to have later menarche (*steroids=13.90yr, no steroids=13.20yr, p=0.017*).

In a stepwise regression analysis, pre-puberty BMI was the only variable to predict age of menarche for both groups (*SN: β=-0.43, p=0.016; C: β=-0.43, p=0.003*) accounting for approximately 17% of the variance. The use of steroids was also significant when data for short and control girls were combined and accounted for an additional 5% of the variance.

4.4.4 Duration of puberty

The duration of puberty correlated negatively with the age at take-off for short (*r=-0.52, p<0.001)* and control (*r=-0.73, p<0.001*) groups separately, and for both groups combined (*r=-0.52, p<0.001)*. The earlier the spurt occurred, the longer it lasted. For short and control girls together, the mean duration decreased by approximately 6 months for each advancing year (*β=-0.48*). In a stepwise regression analysis, no other variable was found to correlate with or predict the duration of puberty for either group or for both groups combined.

4.4.5 Height gain

Height gain during the adolescent spurt depends on both the magnitude and on the duration. It was not surprising then to find that for both groups, height gain correlated strongly with duration (*SN: r=0.90, p<0.001; C: r=0.93, p<0.001*) and to a lesser extent with the magnitude of PHV (*SN: r=0.45, p=0.003; C: r=0.40, p=0.003*). No other genetic or environmental variable was found to correlate with or predict pubertal height gain for either group or for both groups combined.

Table 4:4 *Predictors of the timing, magnitude and duration of the pubertal spurt for a) short and control girls and b) short and control boys*

	VARIABLES ENTERED					
	SHORT	**R^2**	**CONTROL**	**R^2**	**ALL**	**R^2**
a) GIRLS						
Age at PHV	-		1. Height at age 8 years	*0.10*	1. Steroid treatment	*0.053*
PHV	-		-		-	
Duration	-		-		-	
Height Gain	-		-		-	
b) BOYS						
Age at PHV	1. Short for Parents	*0.118*	1. Short for Parents 2. Prematurity	*0.445*	1. Short for Parents 2. Birth weight SDS	*0.311*
PHV	1. Bone age delay	*0.089*	1. Prematurity 2. Birth weight SDS	*0.227*	-	
Duration	1. Prematurity	*0.105*	1. Atopy	*0.072*	-	
Height Gain	1. Maternal Smoking	*0.131*	1. Prematurity	*0.107*	1.Short for Parents 2. Maternal Smoking 3. Pre-puberty BMI	*0.145*

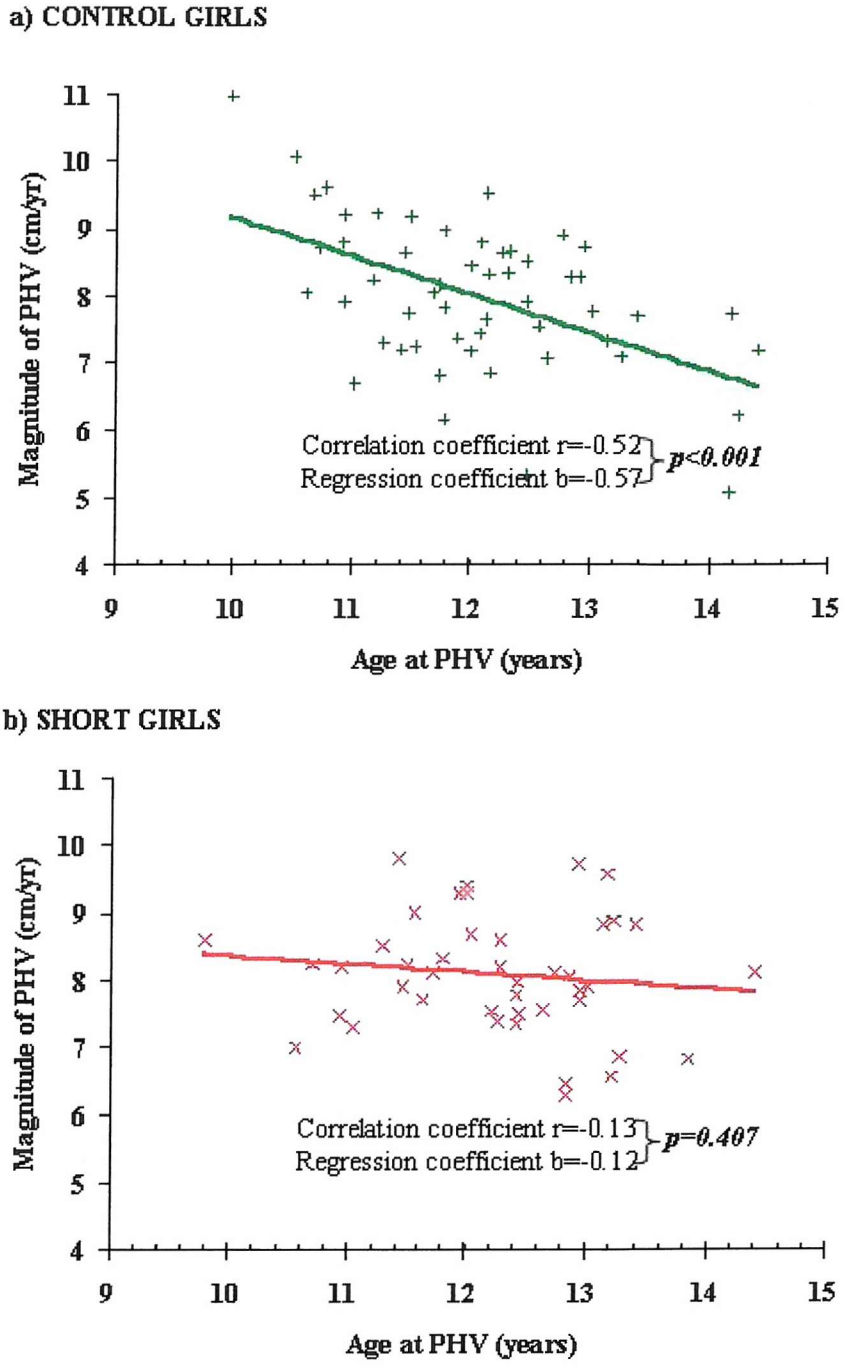


Figure 4.7 *The relation between age at PHV and magnitude of PHV for (a) control girls and (b) short girls*

4.5 The pubertal growth of boys

4.5.1 Genetic, environmental and health profile

A comparison between short and control groups of the genetic, environmental and health variables as reported by parents when the boys were between 12 and 14.5 years is shown in table 4:5. The differences found between short and control boys were similar to those between short and control girls.

Although the mean birth weight of the short group was significantly less than that of the control group, no other differences were found in their birth history. The short boys did have shorter parents than the controls but they were still more likely to be classified as having non-FSS. Indeed, at recruitment 29 (50%) of the short boys were considered to be inappropriately short for parents compared to only 2 (3%) of the controls ($p<0.001$). This did not appear to be a result of social disadvantage. The social class distribution was similar and just as many control boys came from benefit dependent families (table 4:5).

No significant differences were found between the numbers of short and control boys reported to have atopic disease (asthma, eczema, hay fever, or allergies). Twenty-three (39%) of short and 18 (28%) of control boys had at least one condition ($p=0.252$), which was considered severe enough to require steroid treatment in 12 (52%) short and 12 (67%) control boys, respectively ($p=0.524$).

At recruitment, the mean height of the short boys lay on the 0.4th centile (*-2.68 ±0.37 SDS*) and all had heights below the 2nd centile according to the 1990 UK data. By comparison, the mean height of the control boys lay on the 48th centile (*-0.04 ±0.67 SDS*) and ranged from the 6th to 90th centile. For both groups the mean weight centile was similar to the mean height centile (*SN=0.5th centile, C=43rd centile*). The pre-puberty baseline data, recorded when the boys were aged eight years, are shown in table 4:5. During the prepubertal phase of growth, some children improved their height centile and five short boys had a height above the 2nd centile at this age. These included the two boys who had demonstrated catch-up growth shortly after recruitment (see 3.4).

Table 4:5 *Genetic, environmental and health profile of short and control boys*

	SHORT BOYS			CONTROL BOYS			
	Mean	**SD**	**N**	**Mean**	**SD**	**N**	***p-value***
Birth details							
Birth weight (gm)	2840	660	59	3488	512	63	*<0.001*
Birth weight SD*	-0.95	1.04	59	0.29	1.28	63	*<0.001*
Gestation							
Full term >36wks			50 (85%)			58 (91%)	*0.411*
Premature <=36wks			9 (15%)			6 (9%)	
Birth order*							
First born			34 (58%)			36 (56%)	*1.000*
Other			25 (42%)			28 (44%)	
Mothers Smoking*							
Yes			23 (41%)			16 (26%)	*0.116*
No			33 (59%)			46 (74%)	
Parental height							
Target height (cm)	158.0	4.4	58	177.4	4.0	60	*<0.001*
Target height SD	-1.50	0.64	58	-0.12	0.58	60	*<0.001*
Target – Initial Ht SD	1.19	0.70	58	-0.05	0.75	60	*<0.001*
Social Class*							
A & B			10 (17%)			17 (27%)	*0.245*
C_1			6 (10%)			9 (14%)	
C_2			18 (31%)			22 (34%)	
D			15 (26%)			7 (11%)	
E			9 (16%)			9 (14%)	
Reported atopic disease (mean age 13.5 years)							
Eczema							
Yes			12 (20%)			5 (8%)	*0.066*
No			47 (78%)			59 (92%)	
Asthma							
Yes			12 (20%)			8 (13%)	*0.328*
No			47 (80%)			56 (87%)	
Hay fever							
Yes			7 (12%)			12 (19%)	*0.327*
No			52 (88%)			52 (81%)	
Allergies							
Yes			3 (5%)			1 (2%)	*0.349*
No			56 (95%)			63 (98%)	
Atopy * (1 or more condition)			23 (39%)			18 (28%)	*0.252*
Steroid Treatment*			13 (22%)			13 (20%)	*1.000*
Inhaled			2			6	
Topical			4			4	
Both			7			3	
Pre-puberty height & weight (aged 8 years)							
Pre-puberty height SDS*	-2.52	0.43	60	0.00	0.68	64	*<0.001*
Pre-puberty weight SDS	-2.15	0.98	60	-0.04	0.82	63	*<0.001*
Pre-puberty BMI SDS*	-0.52	1.00	60	-0.11	0.88	63	*0.017*

*The variables marked with * were examined in stepwise multiple regression analysis to determine predictors of age and magnitude of PHV. For the short group, bone age at recruitment was also considered*

Compared with Tanner's standards (mean delay ±SD = 0±1.0 years) [Tanner 1983b], the initial mean bone age delay of the short boys was 0.70 ±0.88 years and 19 (39%) were delayed by more than one year.

4.5.2 The mean pubertal spurt

Figure 4.8 shows the mean pubertal growth spurt adjusted for age of PHV of short and control boys plotted against Tanner's standards. Before puberty, the short boys grew more slowly than controls, confirming Bailey's (1994) observation that height velocity of prepubertal children is conditional on initial height.

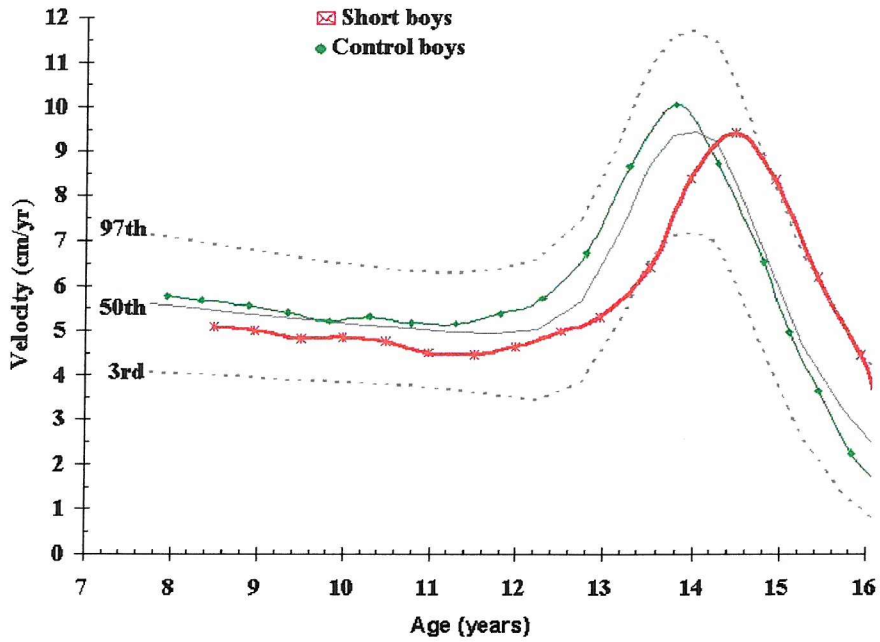


Figure 4.8 *Height velocity, adjusted for age at PHV, of 60 short and 64 control boys plotted against Tanner's standards*

As discussed previously, the prepubertal growth of short normal girls paralleled that of the control girls but significant differences were found between the short and control boys in this study (table 4:3b). Although the mean (SD) duration was similar for both groups (*SN: 5.08 (0.85) years, C: 5.05 (0.79) years, p=0.778,* the age at the onset of the pubertal spurt, the age at PHV, and the age at completion occurred, on average, approximately 8 months later for the short boys. The magnitude of the PHV was also somewhat less for the short boys though the difference did not reach statistical significance (table 4:3b). During the pubertal spurt, the

mean height gain for the short boys was 30.5cm compared to 32.4cm for the control boys ($p=0.067$).

Both prepubertally and during the pubertal spurt, short boys gained less weight than the controls (figure 4.9). The mean gain in weight during the puberty was 22.8kg for short boys and 29.6kg for the control boys ($p<0.001$).

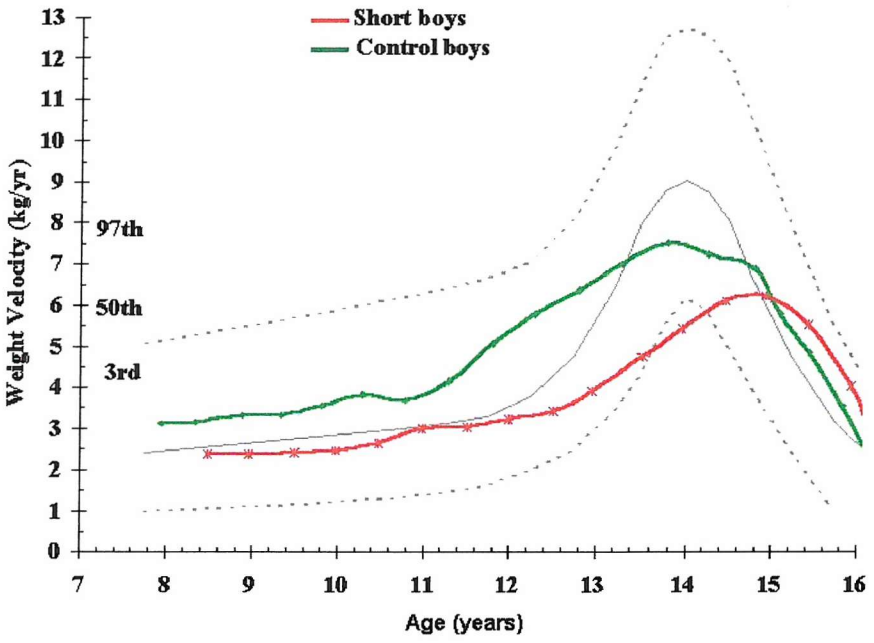
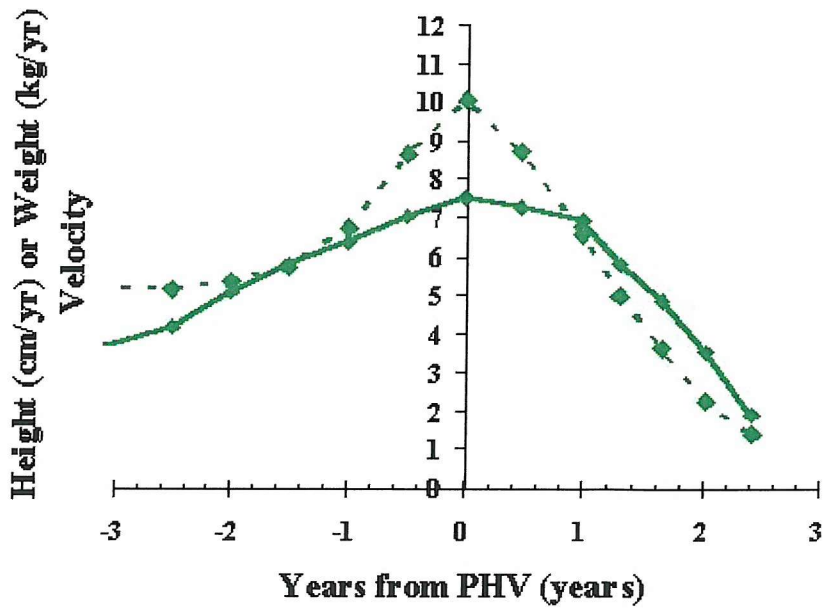


Figure 4.9 *Weight velocity, adjusted for age at PHV, of short and control boys plotted against Tanner's standards*

Differences were also observed in the pattern of weight gain of both groups (figure 4.10). For the control boys a sharp rise in weight gain took place in the year before take-off and maximum weight gain corresponded with the age at PHV (figure 4.10a). For the short group, however, the adolescent spurt was not preceded by a spurt in weight and maximum weight gain occurred 6 months ***after*** the age at PHV (figure 4.10b).

a) CONTROL BOYS



a) SHORT BOYS

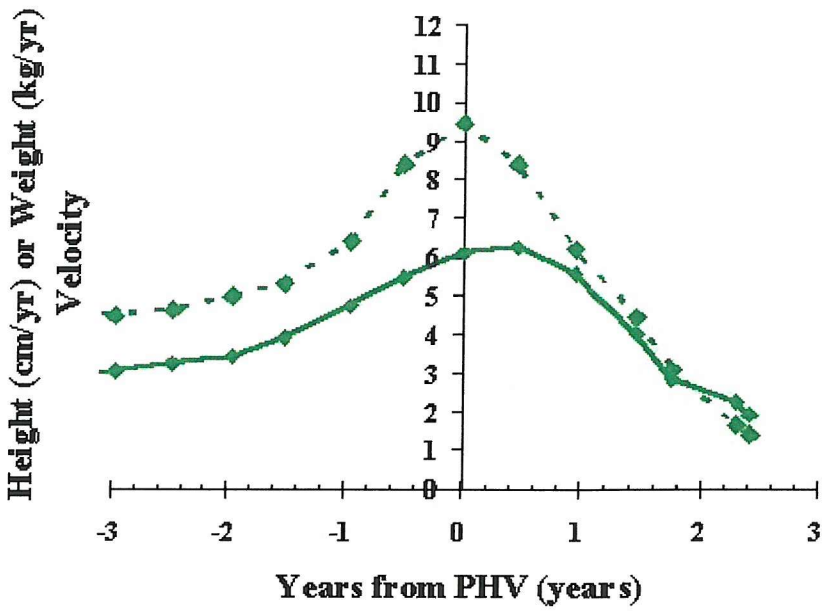


Figure 4.10 *Pattern of weight gain(——) in relation to height gain(- - -) during the adolescent spurt for a) control boys and b) short boys*

4.5.3 Individual Variation

Figures 4.11 and 4.12 show the individual variation in age at PHV and magnitude of PHV.

Peak height velocity

Some differences in the distribution of age at PHV were observed (figure 4.11). Control boys were more likely than those who were short to experience PHV before the age of 14 years (*SN: 22(37%), C: 43(68%), p=0.*001) and it occurred earlier than Tanner's 3rd centile for 5 (8%) control but no short boys. However, in both groups puberty was just as likely to be delayed beyond the 97th centile with PHV occurring after this point for 8 (13%) short and 7 (11%) control boys (*p=0.578*). The 8 short boys included all those who had been prescribed oxandrolone even if PHV occurred before this point, as was the case for two of these boys (figure 4.11).

The magnitude of PHV fell outside Tanner's 3rd to 97th centile norms for a similar proportion of short and control boys (figure 4.12). PHV was above the 97th centile for 9 (4 SN, 5 C) boys while 5 (3SN, 2 C) had a peak that was less than the 3rd centile.

Duration and height gain

Although puberty occurred later for the short group, there was no difference in the mean duration, defined as the period from age at takeoff, through PHV until height velocity fell below 3cm/yr. Compared with the girls, the pubertal spurt lasted slightly longer with the overall the mean duration (SD) for boys being approximately 5.0 (1) years. Again wide individual variation was observed but the adolescent growth spurt lasted between 3 and 7 years for most boys (figure 4.13).

Height gained during the adolescent spurt ranged from 15.5cm to 42.8cm for the short boys and from 15.9cm to 47.4cm for the controls.

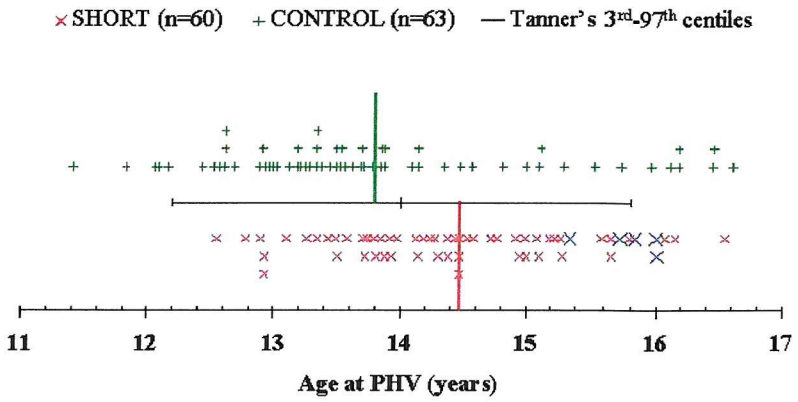


Figure 4.11 *The age at peak height velocity for each short and control boy plotted against Tanner's standards. The 5 boys prescribed oxandrolone are represented by* **X**

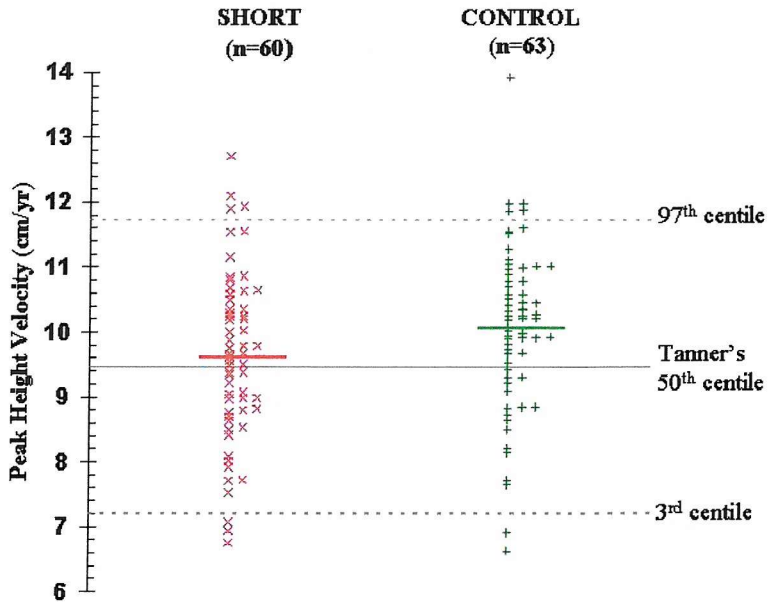


Figure 4.12 *The magnitude of peak height velocity for each short and control boy plotted against Tanner's standards*

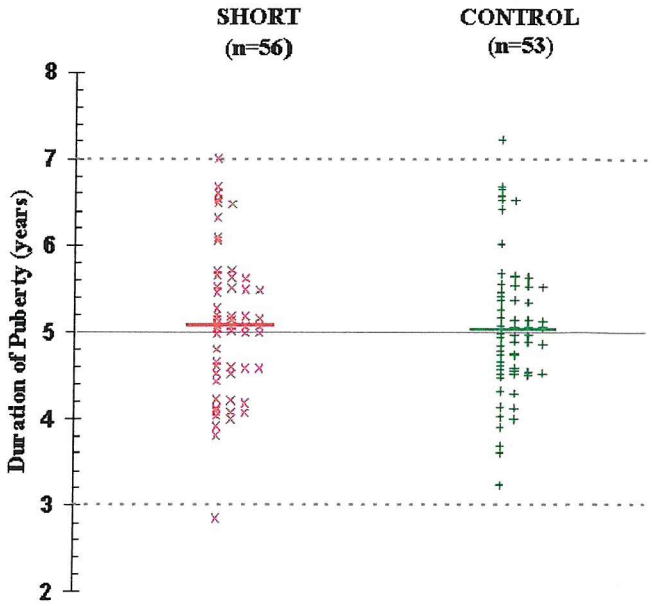


Figure 4.13 *Individual variation in the duration of puberty for short and control boys*

4.6 Factors influencing pubertal growth of boys

The genetic and environmental variables indicated in table 4:5 were examined in a stepwise multiple regression analysis to determine their influence on pubertal development. A summary of the predictors of the timing, magnitude and duration of the spurt are shown in table 4:4b.

4.6.1 Age at PHV

The factors influencing the age at PHV for boys differed from those of the girls. There was again a modest but significant negative correlation between age at PHV and pre-puberty height for the control boys ($r=-0.28$, $p=0.026$) but atopic conditions and its treatment did not appear to have the same effect on the progress of puberty in boys as it did in girls. In both groups, there was a significant correlation between the age at PHV and the presence of asthma but this was ***positive*** for the short group ($r=0.29$, $p=0.026$) and ***negative*** for the controls ($r=-0.29$, $p=0.022$). Although boys were just as likely as girls to receive steroid treatment, this did not appear to delay puberty even when both groups were combined.

Several genetic variables, however, did correlate significantly with age at PHV for both groups. For both short and control boys, those with taller parents tended to reach PHV later. The correlation between age at PHV and parental target height was *0.32, p=0.016* for the short boys and *0.35, p=0.006* for the controls. At recruitment, the height range of the short boys was narrow and, as might be expected, the discrepancy between height SD at recruitment and parental height SD was also significant for this group (*r=0.34, p=0.008)*. However, although the range of initial heights among the control boys was wide (6th to 90th centile), a similar significant relationship was also evident (*r=0.53, p<0.001).* Regardless of their height group, boys who were shortest for parents were more likely to have a later pubertal spurt (figure 4.14).

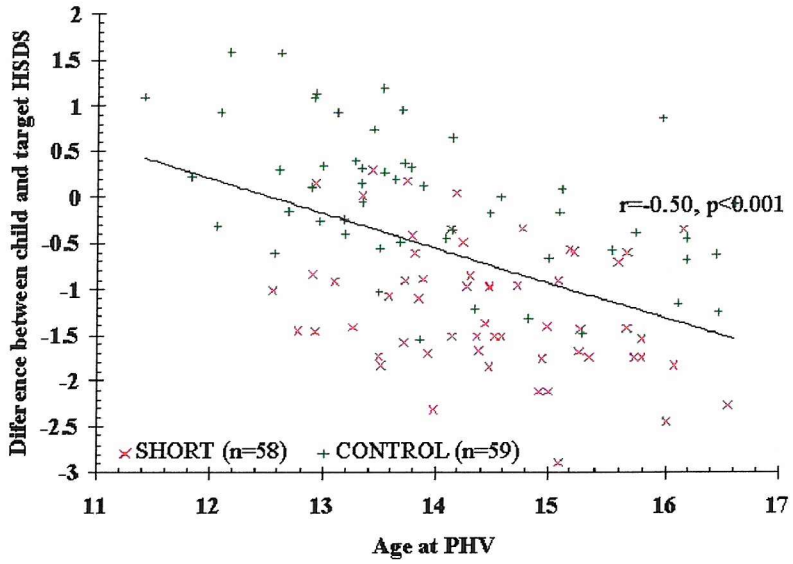


Figure 4.14 *Boys, short or control, who were shortest for parents tended to be the most delayed*

Birth factors also appeared to play a part in the timing of male puberty: age at PHV correlated significantly with birth weight (*r=0.31, p=0.017*) for the short group, and with gestational age for the control group (*r=-0.35, p=0.004*). For the control boys only, those born prematurely, before 37 weeks gestation, tended to have a later PHV (<37 weeks*: 15.48yrs, ≥37 weeks: 13.62yrs, p<0.001*).

To eliminate any possible confounding effects, a stepwise regression analysis was performed using the variables indicated in table 4:5. The discrepancy between height at recruitment and parental height predicted the age of PHV for short and control boys separately and when the groups were combined accounting for 12%, 28% and 25% of the variance, respectively. No other variable was entered for the short group but prematurity was also a significant predictor for the control group explaining a further 17% of the variance. When the groups were combined, birth weight SD score was also entered, accounting for an additional 5% of the variance.

4.6.2 Magnitude of PHV

Figure 4.15 shows the relation between age and magnitude of PHV for short and control boys. Results were similar to those of the girls. No significant relationship was found for the short boys but the correlation (*r=-0.60*) and hence regression (*β=-0.62*) of PHV on age of occurrence were highly significant for the control boys and similar to Tanner's values of r=-0.47, β=-0.77. Those with later peaks had lower PHV.

It has already been observed that the pubertal spurt of control boys born prematurely was significantly delayed. It was not then surprising that these boys also had a significantly reduced peak (*<37 weeks: 8.6cm/yr, ≥37 weeks: 10.2cm/yr, p=0.003*). Indeed, in a stepwise regression analysis prematurity accounted for 14% of the variance in the magnitude of PHV for control boys (table 4:4b).

For the short girls, bone age delay was not predictive of either the magnitude or timing of PHV. However, for the short boys, bone age delay was significantly correlated with the magnitude of peak (*r=0.30*) though not for the age at its occurrence. Those with the most delay had the highest peaks. Indeed, although it accounted for only 9% of the variance, this was the only variable to predict the magnitude of the PHV for short boys.

When the groups were combined, no variable was found to correlate with or predict the magnitude of PHV.

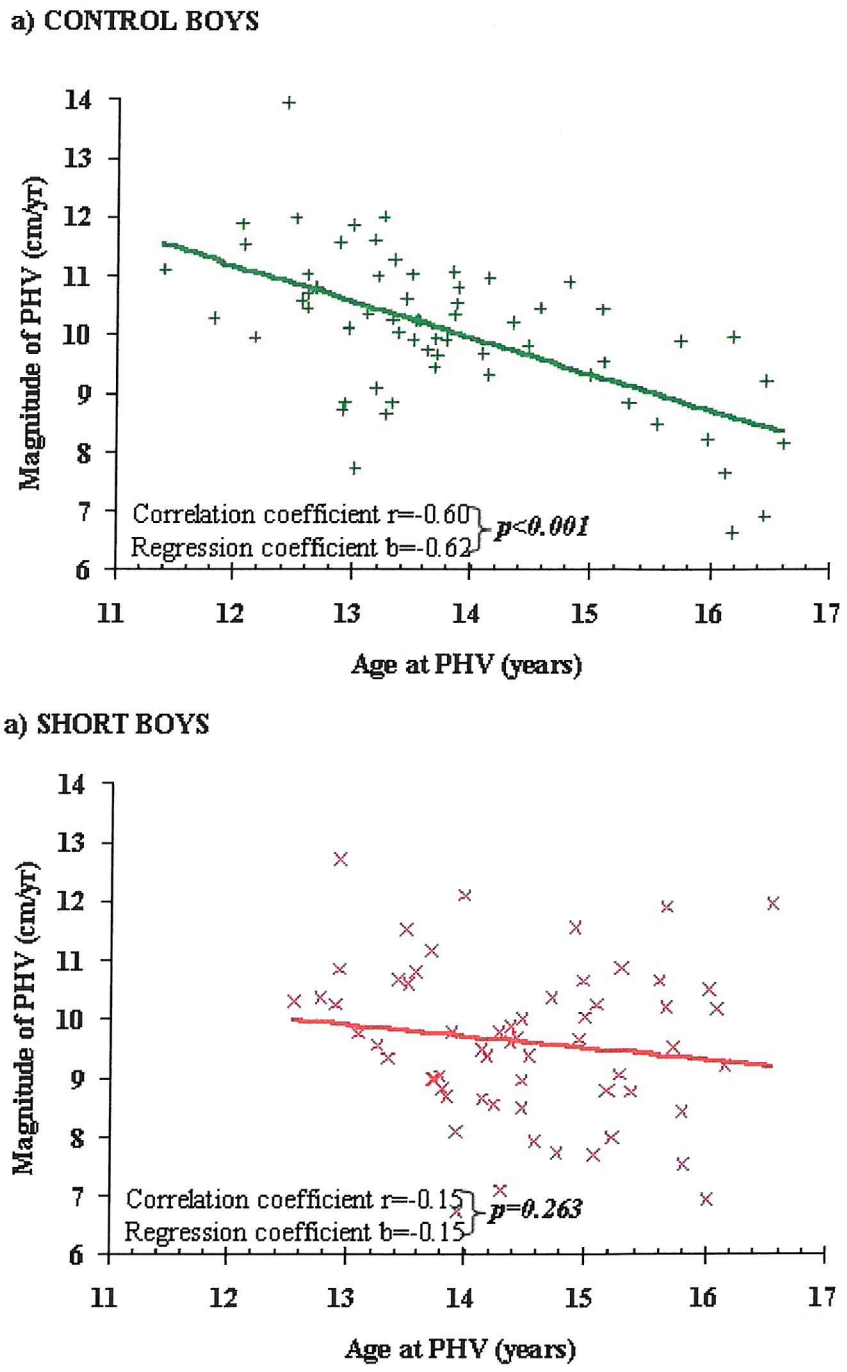


Figure 4.15 *The relation between age at PHV and magnitude of PHV for (a) control and (b) short boys*

4.6.3 Duration of puberty

For both groups of boys, the duration of puberty again correlated with age at take-off (*SN: $r=-0.60$, $p<0.001$; C: $r=-0.65$, $p<0.001$*). Those with the earliest spurts tended also to have the longest. When the groups were combined, the mean duration decreased by approximately 5 months for each advancing year (*$\beta=-0.38$*). In a stepwise multiple regression analysis examining the variables indicated in table 4:5, prematurity was found to be a predictor of the duration of puberty for short boys and the presence of atopy for the control boys. The duration of puberty was significantly longer for short boys born before 37 weeks gestation (*<37 weeks: 5.69yr, ≥37 weeks: 4.95yr, $p=0.016$*) and significantly shorter for control boys with one or more atopic condition (*atopy: 4.39yr, no atopy: 5.15yr, $p=0.039$*). However, when the data for both groups were combined, no variable was found to predict the duration of puberty (table 4:4b).

4.6.4 Height gain

The relation between the timing and magnitude of puberty and the adolescent height gain was similar to those of the girls in the study. For both short and control boys, height gain correlated strongly with duration (*SN: $r=0.87$, $p<0.001$; C: $r=0.87$, $p<0.001$*) and to lesser extent with the magnitude of PHV (*SN: $r=0.46$, $p<0.001$; C: $r=0.58$, $p<0.001$*).

Step-wise multiple regression analysis were performed to eliminate confounding variables and determine biological and environmental predictors of adolescent height gain. The results are summarised in table 4:4b. For the short normal group, maternal smoking during pregnancy accounted for 13% of the variance while in the control group the presence of atopy explained 11% of the variance. Pubertal height gain was greater for those short boys whose mother smoked during pregnancy and less for control boys with atopic conditions. When the data for both groups were combined, shortness for parents, maternal smoking during pregnancy and body mass index at the age of eight were entered. Overweight prepubertal boys and those who were shortest for parents tended to gain less height during puberty. Again, rather surprisingly, short and control boys whose mother smoked during pregnancy tended to show evidence of catch-up growth during the adolescent spurt. These three variables in total accounted for 15% of the variance in adolescent height gain.

4.7 Comparison with other studies

Where possible, the mean values of the magnitude of PHV, age at take-off, age at PHV and age at the completion of the spurt were compared with other studies. As no differences were found between short and control girls for any pubertal parameter, the data for both groups were combined. Short boys and control boys were compared separately. Results are shown in table 4:6.

Table 4:6 *Comparison of the pubertal spurt parameters from different investigations: mean values and standard deviations*

	Age at Take-off (years)	Age at PHV (years)	Magnitude of PHV (cm/yr)	Age at Completion (years)
a) Girls				
Wessex Growth Study	9.75 (1.17)	12.13 (0.98)	8.04 (1.01)	14.30 (0.89)
Tanner et al 1976	10.30 (0.95)	11.89 (0.90)	8.13 (0.78)	-
Preece & Baines 1978	9.05 (0.82)	12.01 (0.85)	7.50 (0.76)	-
Largo et al 1978	9.6 (1.1)	12.2 (1.0)	7.1 (1.0)	13.5 (1.1)
Taranger et al 1976/80	9.49 (1.25)	11.98 (1.02)	8.58 (1.15)	14.82 (0.88)
Gasser et al 1985	9.7 (0.96)	12.2 (0.81)	7.0 (0.95)	13.8 (0.84)
Buckler 1990	-	12.10 (0.98)	8.08 (1.07)	-
b) Boys				
Wessex Growth Study				
Controls	11.12 (1.35)	13.80 (1.25)	10.06 (1.28)	16.13 (1.01)
Short	11.73 (1.18)	14.47 (0.97)	9.61 (1.30)	16.78 (0.94)
Tanner et al 1976	12.05 (0.85)	13.91 (0.84)	8.80 (1.05)	-
Preece & Baines 1978	11.15 (1.05)	14.36 (0.99)	8.72 (1.03)	-
Largo et al 1978	11.0 (1.2)	13.9 (0.8)	9.0 (1.1)	15.5 (0.9)
Taranger et al 1976/80	11.55 (1.37)	14.07 (1.08)	9.93 (1.14)	17.05 (0.98)
Gasser et al 1985	10.9 (1.1)	13.9 (0.95)	8.3 (0.82)	15.4 (0.91)
Buckler 1990	-	14.14 (0.96)	9.83 (1.24)	-

These values are based on different samples of subjects using different statistical methods: most have used some form of curve fitting to obtain parameter estimates although Taranger and Hagg (1980) have relied on visual inspection of the height velocity curve. Nevertheless,

there was general agreement among the studies that age at PHV occurred at approximately 12 and 14 years of age for girls and boys, respectively.

There was more variation among the studies regarding both age at take-off and age at completion of the spurt. For most individuals, the adolescent peak is clearly visible from the height velocity curve. The age at take-off, however, where prepubertal deceleration changes to into adolescent acceleration, is less obvious. In the years preceding puberty, there is little variation in the growth rate and so the error inherent in height measurement or transient fluctuations in growth rate makes this crossover point more difficult to determine.

Nevertheless, while agreed definitions do exist for both age at PHV and the age at takeoff, there is less consistency among authors regarding the end of the pubertal spurt. Largo et al (1978) chose to define this point as the age at which growth velocity returned to the minimal prepubertal velocity. Such a definition may produce bias when comparing groups of different heights since before puberty, the height velocity of a short child is somewhat less than that of a child of average height [Bailey 1994]. Others have arbitrarily chosen definitions based on age [Tanaka et al 1988], percentage of final height [Buckler 1990, Vizmanos et al 2001], or absolute velocity [Taranger and Hagg 1980]. In the present study, the end of puberty was taken to be the age after PHV when height velocity dropped below 3cm/yr. For girls this occurred, on average, at 14.30 years, slightly earlier than that reported by Taranger and Hagg (1980) who chose an end point velocity of 2cm/yr.

There was also more disagreement between studies as to the magnitude of the peak. These differences are likely to be the result of different methodology rather than sample diversity. In some studies, estimates were obtained from 3-monthly height measurement while in others the measurement interval was 6 months. During the adolescent spurt, growth rate changes from acceleration to deceleration in a very short period of time. Longer intervals will have a flattening effect. Furthermore, estimates of the PHV are consistently found to be higher when obtained by graphical methods rather than curve fitting techniques. For example, using mathematical modelling techniques, Preece and Baines (1978) reported estimates of PHV ranging from 7.58 to 7.92 cm/yr for girls, and from 8.62 to 9.11 cm/yr for boys while graphical estimates yielded 8.32 cm/yr and 9.62cm/yr, respectively. The same authors admit that the one parameter their models do not fit well is the magnitude of peak height velocity. In the present study, PHV was estimated from 6-monthy height measurements using a

combination of graphical and simple mathematical techniques (see 2.7). This method is likely to produce a value that is close to the graphical estimate but lower than the true instantaneous peak.

4.8 Discussion

Secular Trend

It has been suggested that the secular trend towards increasing height in the UK reflects a trend towards earlier maturity [Freeman et al 1995]. However, no evidence of this was found for either girls or boys in the Wessex Growth Study. For both short and control girls, the mean values for age at PHV and age at menarche were close to Tanner's original standards [Tanner et al 1966a, Tanner et al 1966b]. The mean age at PHV for the control boys was also near Tanner's mean value while short boys tended to have a later pubertal spurt. These findings are likely to be a true reflection of the timing of puberty in the UK. Tanner's pubertal standards were constructed over 30 years ago from the data of 41 girls and 49 boys and the values in the present study were derived from a similar number of short (46 girls, 60 boys) and control (55 girls, 63 boys) subjects. All social groups were included, and the distribution of social class was comparable to the national average [Downie et al 1997].

Although a positive secular change in stature is often accompanied by an earlier pubertal spurt [de Muinck Keizer-Schrama and Mul 2001], taller adult stature may also be the result of increased prepubertal growth or a more intense period of pubertal growth. There is some evidence to suggest that pubertal growth is now more intense, at least for the boys in this study. As discussed previously, estimates of PHV and adolescent height gain are subject to methodological differences. Nevertheless, compared with Tanner's mean values, the magnitude of PHV was slightly lower for the girls in the study and slightly higher for the boys (table 4:3). Moreover, while the mean height gain for the girls was similar to that previously reported by Tanner et al (1976), the boys gained approximately 4cm more. Two recent nationwide growth surveys conducted in Europe have observed similar trends. In the UK, the overall increase in stature between 1966 and 1990 was found to be similar for both genders at the age of 5 years but more pronounced among males at adult height [Freeman et al 1995]. For Dutch boys and girls, most of the secular height increase occurred prepubertally but further increases up to final height were also noted for boys [Fredriks et al 2000].

Body Composition

The adolescent spurt of short boys was somewhat delayed compared with both Tanner's standards and with the control group (figure 4.8). Given the shortness of their stature and the number with non-FSS (table 4:5), this was not surprising. Both these factors are reported to be associated with delayed pubertal development [Rekers-Mombarg et al 1996]. However, although short girls had similar initial heights as short boys and they were just as likely to be short for parents, these data clearly show that the timing, magnitude and duration of their pubertal spurt are comparable to Tanner's mean and to the control girls.

The factors that initiate the onset of puberty remain elusive [Terasawa and Fernandez 2001] and the reason for this gender difference among the short children is unclear. One possible explanation may relate to changes in body composition. Puberty is thought to be triggered by a rise in subcutaneous body fat [Vizmanos and Marti-Henneberg 2000]. Body fat, particularly subcutaneous fat, is correlated with leptin and, in recent years, the importance of leptin for the progression and regulation of puberty has been recognised [Ong et al 1999, Clayton and Trueman 2000, Chehab 2000]. For both males and females, leptin levels rise around the age at puberty, perhaps as a result of a rise in subcutaneous body fat. No direct measures of body fat were available in this study, but it is interesting to note that the short boys were the only group not to display an increase in weight gain before the adolescent spurt. Shortly before pubertal onset, the girls in both height groups displayed a mini-spurt in weight (figure 4.2) while a sharp rise in weight gain occurred for control boys (figure 4.9). Whether this resulted in an increase in fat or lean mass is unknown but it may account for the delay in pubertal onset of the short boys.

Menarche occurred after PHV and those girls, short and control, with higher pre-puberty BMI tended to have earlier menarche. It has been hypothesised that although maturation is triggered and regulated by the endocrine system, it may be altered by external events, such as body composition [Scott and Johnson 1982]. Fat tissue is thought to increase oestrogen levels and stimulate the maturation process [Cooper et al 1996, Scott and Johnson 1982]. However, there was a moderate and significant negative correlation between age and BMI SDS at menarche ($r=-0.48$, $p<0.001$), which suggests that the importance of excess fat tissue diminishes with age. A large-scale national study also showed that the occurrence of menarche was not only dependent on physical maturation, but also on height, weight and BMI [Mul et al 2001], confirming that the onset of menstruation is a complex interaction of

pubertal development and body size [Elizondo 1992, Scott and Johnson 1982]. It should also be noted that the range of BMI at menarche was wide (15.32 to 29.53 Kg/m^2) demonstrating that a critical amount of body fat is not essential for menarche to occur as has been previously reported [Frishe 1990].

Psychological Stress

Skuse et al (1996) estimated that psychosocial short stature affects 3% of short normal children. This condition has many presenting symptoms and three subtypes have been described [Blizzard and Bulatovic 1992]. During childhood, it is characterised by short stature, poor growth, delayed adolescence and in many cases, adverse birth circumstances [Gohlke et al 1998]. The data from this study suggest that growth retardation due to emotional and social distress is just as prevalent among those who are taller. In both groups, boys who were shortest for parents at the time of recruitment tended to the most delayed (figure 4.14). Birth factors too seemed to play a part in the pubertal development of short and control boys (table 4:4). These data lend some support to the hypothesis that boys may be more vulnerable to negative factors, which are expressed in less than optimal growth [Rudolf and Hochberg 1990]. In a review of the literature, these authors observed the preponderance of boys diagnosed with psychosocial growth retardation and also noted that boys were more vulnerable to stress even before birth.

Constitutional Delay of Growth and Puberty (CGDP)

Peak height velocity occurred after the age of 14 years for twice as many boys in the short group. Nevertheless, control boys were just as likely as short boys were to experience a delay beyond Tanner's 97^{th} centile. Indeed, instead of the expected 3%, more than 1 in 10 boys in both groups experienced a delay beyond this point. Among the clinic population, those diagnosed with CDGP are far more likely to be males than females [Grumbach and Styne 1998]. Referred patients often present with emotional and social difficulties [Albanese and Stanhope 1995]. Whether this is due to short stature or lack of sexual development is uncertain. Apter et al (1981) found that self-imaging was more affected by growth retardation than by delayed sexual development while others have concluded that it is more strongly related to sexual maturity than height [Lewis et al 1977, Lee and Rosenfeld 1987]. In the Wessex Growth Study, five short but no control boys with significant pubertal delay were referred for specialist opinion suggesting that it is shortness of stature rather than the absence of sexual development alone that causes distress and/or concern.

Bone Age

Skeletal maturity in the prepubertal years has been regarded as a measure of the tempo of growth, and bone age delay before puberty taken to indicate CDGP [Tanner 1989]. For the short children in this study, bone age evaluation was made before the age of eight years. No gender differences were found and most were delayed to some extent. The mean delay was less than is usually reported for short normal children referred to growth clinics, but this is not surprising as clinic referred samples tend to be older and with a preponderance of boys [Ranke and Linberg 1994]. Many normal children, especially boys, are referred to growth clinics during the adolescent years when a diagnosis of CDGP, and therefore a significant bone age delay, is likely [Albanese and Stanhope 1995]. In the Wessex Growth Study, bone age SD scores, recorded between five and seven years of age, did not correlate with the timing of puberty ($r=-0.14$, $p=0.212$), calculated by subtracting 12 or 14 from the age at PHV for girls and boys, respectively, or with the age of menarche ($r=-0.08$, $p=0.655$). Nor did stepwise multiple regression analyses find it to be a predictor of age at PHV for either boys or girls, or of menarcheal age in girls. Indeed, Ranke (1996) has confirmed a diagnosis of CDGP may only be established ***after*** the usual age for the onset of puberty.

Although prepubertal bone age assessment cannot predict the timing of puberty, it may still be a useful indicator of future growth [Khamis and Roche 1995]. During the pubertal spurt, the short boys with the most delay did tend to have higher peaks and it may be that an increased height velocity will occur at some point during the growth process for all short children whose bone age is delayed. Prepubertal, pubertal and post-pubertal growth all contribute towards final height. Final height will be investigated in the next chapter to determine if a delayed bone age in the prepubertal years ultimately results in a relative gain in height.

Family Environmental

Although pubertal development is to a large extent genetically programmed, several environmental factors have been associated with the timing of puberty. Low social class and large family size are reported to result in delayed maturation [Tanner 1962, Billewicz et al 1981, Hulanicka and Kotlarz 1983]. Tanner (1986a) also observed an interaction between social class and family size. He concluded that social class differences were almost entirely due to those from large families with fathers in manual occupations. A similar interaction between social class, family size and prepubertal height has also been reported [Rona et al

1978]. It is possible, as Tanner (1992) has postulated, that these observations simply reflect the stress each extra child generates with poorer families less able to cope. Such conditions may well lead to poor nutrition and inadequate child care resulting in a slower tempo of growth throughout childhood. For the children in this study, however, regardless of height group or gender, these factors were ***not*** predictive of the timing of puberty (table 4:4). One possible explanation may be the changing nature of society and family structure. Recent decades have seen major social changes in the UK, which have resulted in better health care for all, an increase in urbanization, and a decrease in family size [Hicks and Allen 1999]. While social class inequalities in health are still apparent [Carter 2002], statistics now show that 25% of children were the only dependent child in the family, regardless of social class [Walker et al 2001].

Age at menarche has also been associated with birth weight, social class, family environment and prepubertal height [Cooper et al 1996, Billewicz et al 1981, Roberts et al 1986, Ulijaszek et al 1991, Tanner 1962, Elizondo 1992] but the data from this study could not confirm these. The mean age was similar for both groups and no genetic or environmental variable was found that could predict menarcheal age for either short or control girls.

Atopic Disease

During the primary school years, the children remained well and no major health problems were reported for either group. Taller children, however, both boys and girls, were ***more*** likely to develop atopic conditions. At recruitment, fewer control children were reported to suffer from asthma or eczema but by early adolescence, no significant differences were found either for the girls or for the boys in the study. Initially, only 5% of control girls were reported to suffer from asthma and 5% from eczema. Similar prevalence rates of 7% for asthma and 4% for eczema were also reported for control boys. At the time of the parental interview in 1995/96 when the children were approaching puberty, these incidences had doubled (tables 4.2 and 4.5). Little change was observed among the short children though some appeared to outgrow the condition while others had been newly diagnosed. Such a phenomenon is not unexpected. Reviewing the evolution of asthma throughout childhood, Sears (1998) observed that early wheezing followed by remission was associated with reduced air flow but not with a family history of asthma or evidence of atopy. Before puberty, shorter children do have a reduced airflow capacity [Rosenthal et al 1993] and it may be this that contributed to much of the reported asthma among the short children at

recruitment. Asthma is more common among boys in early childhood but during adolescence, the prevalence changes from male predominance to female predominance [Sears 1998]. Interestingly, the incidence of asthma at recruitment was highest among the short boys (*SN: boys 22%, girls 13% C: boys 7%, girls 5%, p=0.010*). For both boys and girls, airflow capacity is reduced in shorter children, but, prepubertally, boys have poorer airflow/unit lung volume [Rosenthal et al 1993], which may account for this observation. By early adolescence, however, atopic conditions requiring steroid treatment were just as likely regardless of height group and gender (tables 4.2 and 4.5).

In community samples, such as this, where there have been few measures of disease severity, atopic conditions do not appear to affect height [Power and Manor 1995, McCowan et al 1998]. Delayed pubertal development, however, has been linked with atopic disease [Albanese and Stanhope 1995, Power and Manor 1995, Balfour-Lynn 1986] and the age at PHV and age at menarche were significantly later for those girls with atopic disease treated with inhaled and/or topical steroids. Whether this delay is due to the severity of the disease or the treatment is unclear. Corticosteroid therapy, however, may well be another external event acting on the endocrine system with a modifying effect as suggested by Hindmarsh et al (1993). Nevertheless, no such effect was observed for the boys in the study, even though they were just as likely as girls to suffer atopic conditions and to receive steroid treatment. The reason for this is unclear but deterioration in asthma control among girls is evident around the time of puberty [Bjornson and Mitchell 2000]. Puberty also impacts on socialization [Alsaker 1996] and, in early adolescence, girls are more susceptible to peer pressure and more likely to engage in harmful behaviours such as smoking, which may aggravate the condition [Boreham and Shaw 2001].

Comparison with other Studies

As discussed in 4.7 and in Chapter 2, differing study designs, research methods and definitions make comparison of pubertal characteristics difficult. Nevertheless, the data from the Wessex Growth Study is in general agreement with previous studies of adolescent growth for the age at pubertal onset, the age at PHV, the magnitude of PHV and the age at completion of puberty (table 4:6). During the construction of the original British standards, Tanner et al (1966a 1966b) found that peak height velocity occurred some two years earlier for girls and the magnitude of the peak was greater for boys, findings which have since been unanimously confirmed. The data from the Wessex Growth study also verify these gender

differences in the timing and size of the pubertal spurt for both short and average height children (table 4:6).

Indeed, to some extent, these data demonstrate the normality of adolescent growth for the short children in this study. The magnitude, duration and adolescent height gain were similar for short and control girls, and for short and control boys, although the spurt occurred somewhat later for short boys. These data also show that, regardless of height group or gender, the earlier the spurt occurred, the longer it lasted, a finding confirmed by others [Largo et al 1978, Taranger and Hagg 1980, Gasser et al 1985]. Nevertheless, a higher compensatory peak also normally accompanies earlier maturation [Tanner et al 1976]. Such a relationship was observed for the control children but ***not*** for those who were short (figures 4.7, 4.15).

Adolescent Height Gain

Data from the Wessex Growth Study show that the pubertal spurt lasted longer for boys than for girls (*boys: 5.06 yrs, girls: 4.54 yrs, $p<0.001$*). As a consequence of this longer duration and increased intensity, the adolescent height gain was, on average, 5.5cm less for the girls in the study. However, very little of the difference in adult height between men and women is thought to result from pubertal growth [Tanner et al 1976, Sheehy et al 2000, Gasser et at 2001]. In the present study, the duration of puberty was measured from take-off through PHV until velocity had decreased below 3cm/yr and, at this stage, final height is still to be attained. Several authors have reported a longer period of post-pubertal growth for girls [Largo et al 1978, Taranger and Hagg 1980, Gasser et al 1985]. If this is the case, it is possible that once growth is complete the gender difference in adolescent height gain will diminish. On the other hand, the difference in average height between men and women in the UK has increased from 12.5cm [Tanner et al 1966b] to 14cm [Freeman et al 1990] and, as discussed earlier, there is some evidence that this increase is due to a more intense period of pubertal growth in boys.

Clinical Impact of Pubertal Growth

Before puberty, the height velocity of the short children in the study stayed close to the 25th centile. During puberty this increased to the 50th centile (figures 4.1 & 4.8), although for boys this spurt was somewhat delayed. For the girls in the study, it is unlikely that this relative increase in growth rate will result in a similar gain in height. Simply to remain on the 3rd

centile for height throughout childhood requires growth rate to be close to the 25th centile prepubertally but to be along the 50th centile in the pubertal phase (figure 4.16). It is possible that the increased period of prepubertal growth of the short boys will result in a higher final height centile compared with the short girls, but the outcome in relation to the adult male population is less certain. The earlier pubertal spurt of the control boys was compensated by a larger adolescent height gain.

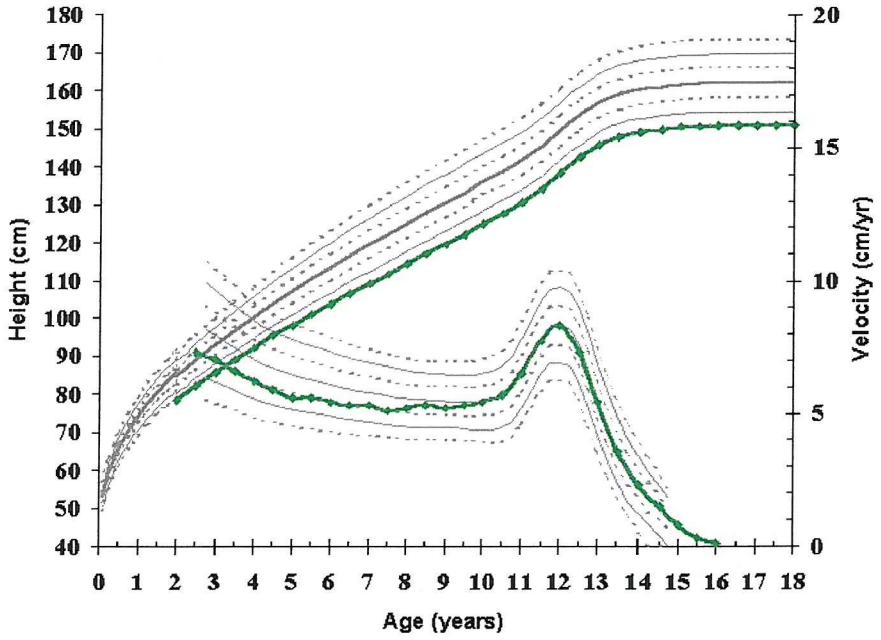


Figure 4.16 *Height velocity required for a girl to remain on the 3rd centile (Tanner & Whitehouse) for height throughout childhood.*

Final height is thought to be independent of the timing of puberty as earlier maturation is generally compensated by a higher adolescent height gain [Tanner et al 1976, Vizmanoz et al 2001], which depends on both the magnitude and the duration of the spurt. Although, regardless of height group, the pubertal spurt tended to last for longer in the earlier maturing child, the higher compensatory peak that normally accompanies earlier maturation was ***not*** observed for the short children (figures 4.7, 4.15). Puberty is marked by a sharp increase in growth velocity, which in the early maturing child results in a transient increase in height centile providing a measure of reassurance to those who are short. The clinician should be aware, however, that the adolescent height gain might not fully compensate for the reduced prepubertal growth of the earlier maturing short normal child.

The ethical aspects, final height outcome and psychological impact of GH treatment are still being debated [Allen DB et al 1994, Downie et al 1996, McCaughey ES et al 1998] but should it be deemed beneficial, the optimum period for treatment must be well before puberty when the potential to increase velocity is greatest.

4.9 Summary

Although both short normal boys and girls have similar genetic backgrounds, only short boys are likely to experience pubertal delay. Short normal girls had similar birth weights, skeletal delay and were just as likely as short normal boys to be identified as having non-FSS but the timing, magnitude and duration of their pubertal spurt are comparable to girls of average height and to Tanner's original standards. On the other hand, the pubertal spurt of short normal boys occurred, on average, some six months later than expected.

The early maturing short child may be most at risk of short adult stature. Although early maturation resulted in a longer period of pubertal growth for both short and control children, only for those of average stature was it also accompanied by a higher compensating peak height velocity. For the short child with early onset of puberty, the adolescent height gain may not fully compensate for the reduced prepubertal growth.

Accurate prediction of pubertal growth would be of value to the clinician in the assessment and treatment of short stature. For the short girls, no variable, genetic or environmental, were found to predict the timing, duration or magnitude of the pubertal growth spurt. There is some evidence to suggest that boys, short and control, are more susceptible to negative factors, which results in slow prepubertal growth and a delayed onset of puberty. In both groups, boys who were shortest for parents at the time of recruitment tended to the most delayed and birth factors seemed to play a part in their pubertal development. For short normal boys, however, these factors accounted for only small amounts of the variance in the timing, magnitude and duration of puberty.

Before puberty, short children grow more slowly than those who are taller and no discernable catch-up growth occurred for the short normal group (see Chapter 3). The magnitude and duration of the pubertal spurt and the adolescent height gain, however, were similar for short and control girls, and for short and control boys ***but*** it is unlikely that this will lead to an

improvement in their relative final height. The relation between final adult height and the height gain before, during and after the adolescent spurt will be explored in Chapter 5.

Chapter 5: ADULT STATURE

Stature growth begins at the moment of conception and ends with epiphyseal closure some two decades later. Height, however, is not accumulated at a fixed rate throughout the growing process. Individuals experience the bulk of their growth in two spurts: during early childhood and adolescence. Nor is the pattern of growth prescriptive. Both the intensity and duration of each phase is subject to wide variation. To a large extent, adult height is determined by parental height, the age at which puberty begins and the intensity and duration of the pubertal growth spurt. Environmental influences are also apparent: much of the secular trend in height observed in Western societies is the result of improved nutrition, health and living conditions. This chapter seeks to explore the effect of prepubertal, pubertal and post-pubertal growth on the adult height of short and control children and determine the extent, if any, of secular trend and catch-up growth. The influence of biological and environmental variables on final height will also be examined.

5.1 Introduction

There is general agreement among published reports that short normal children, in the main, spontaneously become relatively taller adults. Final height, however, is commonly defined in relation to height centile at presentation and there are several reasons why this may not truly be a measure of catch-up growth.

First, many reports are based on children referred during the normal adolescent years and diagnosed with constitutional delay of growth and puberty (CDGP) [Volta et al 1988, Bramswig et al 1990, Crowne et al 1990, 1991, LaFranchi et al 1991, Kalckreuth et al 1991, Sperlich et al 1995, Ferrandez Longas et al 1996]. In such cases, however, growth often slows before the onset of puberty resulting in a transient fall in relative height which is ultimately regained after the completion of the pubertal spurt [Tanner and Davies 1985, Karlberg et al 1987]. Second, recent reports have confirmed a continuing secular trend in height in the UK [Freeman et al 1995] and in other European countries [Fredriks 2000]. Current rates are estimated at 1-3 cm/decade [Cole 2000] and, as growth standards inevitably portray the population on which they were based, children born in the 80's can be expected to be some 2-6cm taller than adults of the 80s. An increase in the relative height of short children may simply reflect an overall increase in the population height. Finally, whenever a

group is chosen based on a biological variable that is extreme on its first measurement, the group mean will tend to be closer to the centre of the distribution on subsequent measurements [Bland and Altman 1994a 1994b]. Inevitably, extremely short children will become, to some extent, relatively taller adults as a result of this statistical phenomenon termed 'regression towards the mean'. Any observed increase in relative height of short normal children may, therefore, be a result of delayed puberty, secular trend, regression towards the mean, or a combination of these variables.

In reality little research has investigated what proportion of prepubertal short normal children experience true catch-up growth and reach a height appropriate for their genetic potential. Rekers-Mombarg et al (1996) attempted to describe the spontaneous growth pattern of children with idiopathic short stature but their sample consisted of 145 boys and 84 girls from nine European countries who had been referred for specialist opinion. Furthermore, much of their data were collected retrospectively, the age at referral is unclear and boys outnumbered girls by almost 2:1. Indeed, since boys present far more commonly with CDGP than girls, there is an overall male preponderance in much of the reported data on final height [Price 1996]. Whether short normal girls generally have the same patterns of growth throughout childhood as short normal boys is unknown.

Nor is it possible to predict adult height from childhood height with any degree of certainty. Four distinct growth phases contribute towards adult stature: foetal growth, infancy, childhood, and puberty [Karlberg 1989]. The growth pathway, however, is not prescriptive and during each phase, individuals vary in both the *rate of maturation and the intensity of growth.* Stature and the tempo of growth are largely genetically determined but many social and environmental factors can have a modifying effect [Tanner 1989, Sinclair 1989]. Consequently, prepubertal children of the same initial heights can have quite different heights as adults.

Data from this study allow these uncertainties to be addressed. The study group consists of all short but otherwise healthy children in a well-defined but wide geographical area together with their age- and gender- matched controls. The children were recruited soon after they entered primary school at the age of 5 years and have since been measured at regular intervals until final height. At school entry, the typical short child had a relatively low birth weight, short parents and was more likely to come from larger families of low socio-

economic class. Many appeared to be inappropriately short for parents but most had some degree of bone age delay and were predicted to have an adult height within the expected range.

The aims of this chapter are first, to explore the effect of prepubertal, pubertal and post-pubertal growth on the adult height of short and control children and determine the extent, if any, of secular trend and catch-up growth; second, to compare the pattern of growth of short normal boys and girls and determine how many short normal children become short normal adults; third, to examine the influence of biological and environmental variables on the final height of short normal children.

5.2 Final adult height

A final height was available for 103 SN (56 boys) and 114 C (62 boys), which represents 74% and 81% of the original sample, respectively. The reasons for the attrition have been discussed in earlier chapters. The short children remaining were representative of the total sample with respect to gender distribution, genetic profile (birth weight, parental height, bone age) and social class (see Chapter 4, table 4:1).

As discussed in Chapter 2, final height and the age at which these occur are difficult to determine precisely (see 2.8). Since the age at which growth stops is somewhat dependent on the timing of the pubertal spurt, final height in this study was considered to be the last recorded measurement provided this occurred ***at least*** three years after peak height velocity (PHV). In effect, only 22 (11%) children (19 boys) were followed for less than 4 years after PHV. The mean interval was 6.44 years for girls and, as a consequence of their later pubertal spurt, 5.03 years for boys.

Even so, height does continue to increase for some time after adolescence. Indeed, increments in stature have been observed up to four years after epiphyseal closure [Garn et al 1961], and as much as ten years after the occurrence of peak height velocity [Roche and Davila 1972]. After the age of 18 years, however, the increase is relatively small and unlikely to affect the final height SD score. The median age at the last recorded measurement was 18.97 years and ranged between 13.75 and 20.86 years. Only 22 (7 boys) subjects were aged less than 18 years. Table 5:1 shows the mean final height SD score for both groups and its relation to the initial height SD score and parental target height SD score.

Table 5:1 *The final height SD scores of 103 short and 114 control children were compared with initial and parental target height SD scores. Values shown are group means (SD). Target height was available for 100 short and 103 control children.*

	SHORT	CONTROL	*p-value*
Final height SD score	-1.96 (0.66)	0.09 (0.74)	*<0.001*
Initial height SD score	-2.65 (0.32)	-0.21 (0.64)	*<0.001*
Change in height SD score	0.69 (0.63)	0.29 (0.60)	*<0.001*
Target height SD score	-1.45 (0.66)	-0.18 (0.63)	*<0.001*
(Final – Target) height SD score	-0.51 (0.77)	0.27 (0.67)	*<0.001*
Number (%) below target height	82 (82%)	45 (42%)	*<0.001*
Number (%) below target range	15 (15%)	0	

5.3 Prepubertal, pubertal and post-pubertal growth

For the reasons presented in Chapter 2, the end of the pubertal spurt in the present study was defined as the point at which height velocity decreased below 3cm/yr after the occurrence of PHV. Consequently, as expected, some growth was observed for most children after this point. The mean (SD) increase in height between the end of the pubertal spurt and final stature was 2.0 (1.1) cm for boys and 2.3 (1.1) cm for girls *(p=0.055)*. As a result, the absolute gain in height from the age of 6 years was considered to have three components; prepubertal gain, pubertal gain and post-pubertal gain. As described in Chapter 2, prepubertal gain was calculated by subtracting height at 6 years from height at take-off, pubertal gain was the height difference between start and end of the pubertal spurt, and post-pubertal gain was the difference between final height and height at the completion of puberty. The mean values for boys and girls in each group are shown in table 5:2.

The post-pubertal height gain was weakly correlated with the time interval between the age at PHV and final height measurement *(r=0.16, p=0.022)* confirming that the amount of the increase depends, to some extent, on the timing of puberty and that, even 3 years after PHV, height continues to increase [Hulanicka and Kotlarz 1983, Hagg and Taranger 1991] However, a linear regression analysis estimated the additional growth to be only 0.14 cm/yr

beyond this 3 year point and most of the cohort had been measured for considerably longer than this.

For both genders, the overall height gain was greater for the control group, but most of this difference occurred before puberty (table 5:2). Indeed, a multivariate analysis examining the effect of gender and height group on height gain at each phase showed that while gender influenced growth in all phases, height group was significant only for height at the age of 6 years (table 5:3). Interestingly, there was a significant group-gender interaction and the univariate *F* tests revealed that this too was the result of height at 6 years. This interaction effect, however, appeared to be the result of a gender difference within the control group (figure 5.1). While the recruitment procedure ensured that short boys and girls were of similar heights at the age of 6 years, control girls were coincidentally slightly shorter than the control boys.

Table 5:2 *The patterns of height gain from the age of 6 years to the attainment of adult stature for a) short and control girls and b) short and control boys.*

	SHORT	**CONTROL**	**Difference**	***p-value***
a) Girls				
Number	43	47		
Height at 6yrs (cm)	102.5 (1.3)	113.2 (2.5)	-10.7	*<0.001*
Prepubertal gain (cm)	19.2 (5.0)	21.5 (7.2)	-2.3	*0.090*
Pubertal gain (cm)	26.4 (4.4)	26.0 (6.2)	0.4	*0.685*
Post-pubertal gain (cm)	2.4 (1.1)	2.2 (1.1)	0.2	*0.654*
Total gain (cm)	48.0 (3.7)	49.8 (3.9)	-1.8	*0.020*
Final height (cm)	150.5 (4.1)	162.9 (4.5)	-12.4	*<0.001*
b) Boys				
Number	55	58		
Height at 6yrs (cm)	103.0 (1.8)	115.8 (3.3)	-12.8	*<0.001*
Prepubertal gain (cm)	29.0 (5.9)	28.7 (6.8)	0.4	*0.815*
Pubertal gain (cm)	30.4 (5.3)	32.6 (5.9)	-2.2	*0.038*
Post-pubertal gain (cm)	2.1 (1.0)	1.8 (1.3)	0.2	*0.335*
Total gain (cm)	61.4 (4.2)	63.2 (3.5)	-1.7	*0.018*
Final height (cm)	164.4 (4.2)	179.0 (5.0)	-14.5	*<0.001*

Table 5:3 *Results of a multivariate analysis examining the effect of gender and height group on each phase of growth*

	Group/Gender		Gender Effect		Group Effect	
	F statistic	**p-value**	**F statistic**	**p-value**	**F statistic**	**p-value**
Hotelling's T^2	2.887	0.024	163.398	<0.001	295.884	<0.001
Height at 6 yrs	9.079	0.003	21.219	<0.001	1182.810	<0.001
Prepubertal gain	2.016	0.157	89.981	<0.001	1.219	0.271
Pubertal gain	3.014	0.084	46.227	<0.001	1.246	0.266
Postpubertal gain	0.095	0.758	4.788	0.030	0.959	0.329

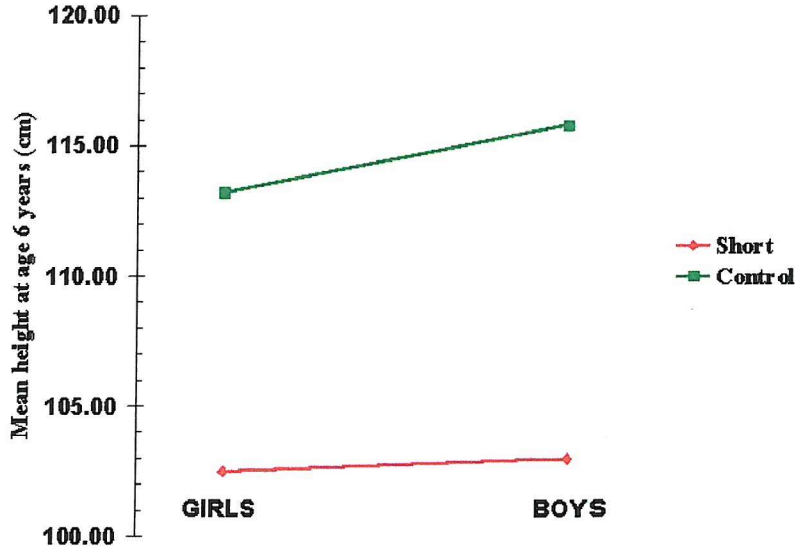


Figure 5.1 *As an artefact of the recruitment procedure, control girls were significantly shorter than control boys at the age of 6 years resulting in a group/gender interaction effect illustrated above*

5.4 Comparison of Short and Control groups

5.4.1 Final height compared with initial height

Significant associations were found between prepubertal height and final height for both groups. For the control group, the correlation coefficient between prepubertal height SD score, recorded at the age of 6 years, and adult height SD score was 0.64, $p<0.001$. This was less than the generally accepted value of 0.8 [Tanner et al 1956]. However, as described in Chapter 2, the controls were chosen from a truncated population sample: recruitment height was restricted to the 10^{th} to 90^{th} centile range according to the standards of Tanner et al (1966a 1966b). Armitage and Berry (1994) have demonstrated that the effect of such a restriction is to decrease the absolute value of the correlation coefficient. Indeed, for the short group the correlation between initial and final height was only 0.34, $p=0.001$.

At recruitment, the mean height of the short children lay on the 0.4^{th} centile and all had a height below the 2^{nd} centile. As a group, the short children grew well and their mean adult height improved by more than a centile band reaching almost the 3^{rd} centile *($p<0.001$)*. By comparison, the mean height of the control group increased from the 42^{nd} centile to the 54^{th} centile *($p<0.001$)*. Although both groups showed a relative improvement in height, the mean difference between initial and final height SD scores was significantly greater for the short children (table 5:1). However, an analysis of covariance investigating the effect of gender and height group revealed a significant gender-group interaction effect *($F=5.87$, $p=0.016$)* illustrated in figure 5.2. In the short group, the relative height gain, or catch-up growth, calculated by subtracting final height SD score from initial height SD score, was greater for boys than for girls *(boys: 0.85 (SEM=0.08), girls: 0.50 (SEM=0.08), $p=0.005$)* but no significant gender difference was found for the control group *(boys: 0.26 (SEM=0.07), girls: 0.32 (SEM=0.09), $p=0.574$)*.

As discussed earlier, at least some of the increase in height centile of the short group may be the result of secular trend. Therefore, before estimating true catch-up growth, any apparent increase in relative height in the short group must be adjusted accordingly. At recruitment, the heights of the control group covered most of the normal range and the mean height centile was close to the population mean. Consequently, regression towards the mean is unlikely to be a significant factor for this group [Davis 1976]. As the 1990 UK growth standards represent the heights of adults measured in the 1980's [Freeman et al 1995], it is reasonable

to assume that any increase in relative height represents secular change and that this would affect both short and control children similarly.

Figure 5.2 *The individual change in height SD score from observed for 103 (56 boys) SN and 114 (62 boys) C during the course of the study. Bars represent the mean change and illustrate the gender-group interaction effect*

Gender differences in the secular increase in height have already been noted, the increase being greater for boys than for girls [Freeman et al 1995, Fredriks et al 2000]. These studies also suggest that much of the overall increase in adult stature occurs before puberty although for boys, but not girls, it may also reflect the effect of an earlier or more intense pubertal spurt. For these reasons, the effect of secular trend on catch-up growth and the pattern of growth were examined for boys and girls separately.

5.4.2 Secular trend in girls

The mean growth patterns of height and height velocity for both groups are shown in figure 5.3a. Height has been plotted against the 1990 cross-sectional reference data [Freeman et al 1995] and height velocity against the cross-sectional whole-year velocity standards of Tanner et al (1966b).

At the age of 6 years, the mean height centile of the short and control girls lay on the 0.4th centile and 34th centiles, respectively, and the mean difference in height was 10.7cm (table 5:2a). The centile lines on the growth charts diverge during childhood and, had both groups remained on their initial height centile, a final height difference of 13.5cm would have ensued. During the course of the study, the mean height centile of the short group increased reaching almost the 2nd centile, equivalent to an increase in final height of 3.0cm. However, the mean height centile of the control girls also increased to just below the 50th centile representing a population increase in female stature of approximately 1.9cm since the construction of the charts. As a result, the mean difference in final height between short and control girls was 12.4cm (table 5:2a). Thus, any improvement in relative height for the short girls with respect to the population is likely to in the order of only 1cm. The mean increase in height SD score was, in fact, comparable for both groups *(SN: 0.50, C: 0.32, $p=0.162$)* and the pattern of height gain was also very similar for short and control girls (table 5:2a).

Certainly, as a group, no discernible catch-up occurred for the short girls during puberty. The characteristics of the adolescent spurt were examined in Chapter 4 and no significant differences were found in the timing, magnitude and duration for the girls in the study. Nor is the secular increase in female stature likely to be the result of a more intense pubertal spurt. For both groups, height increased by approximately 26cm during the pubertal spurt (table 5:2a) and, almost 30 years earlier, Tanner et al (1976) reported a mean adolescent height gain of 25.3 cm.

As shown in table 5:2a, the overall height gain from the age of 6 years until the attainment of adult height was greater for the control group mainly as a result of prepubertal growth, but this was not unexpected given the diverging nature of the centile lines. Simply to remain on their height centile, taller prepubertal children need to grow at a higher rate that those who are short [Bailey 1994]. Using the 1990 UK growth standards, it can be estimated that a 34th centile girl needs to gain around 3cm more than a girl on the 0.4th centile. Before the start of the adolescent spurt the taller controls gained, on average, only 2.3 cm more in height than those who were short (table 5:2a). If indeed any catch-up growth did occur, it is likely that this took place during the prepubertal years.

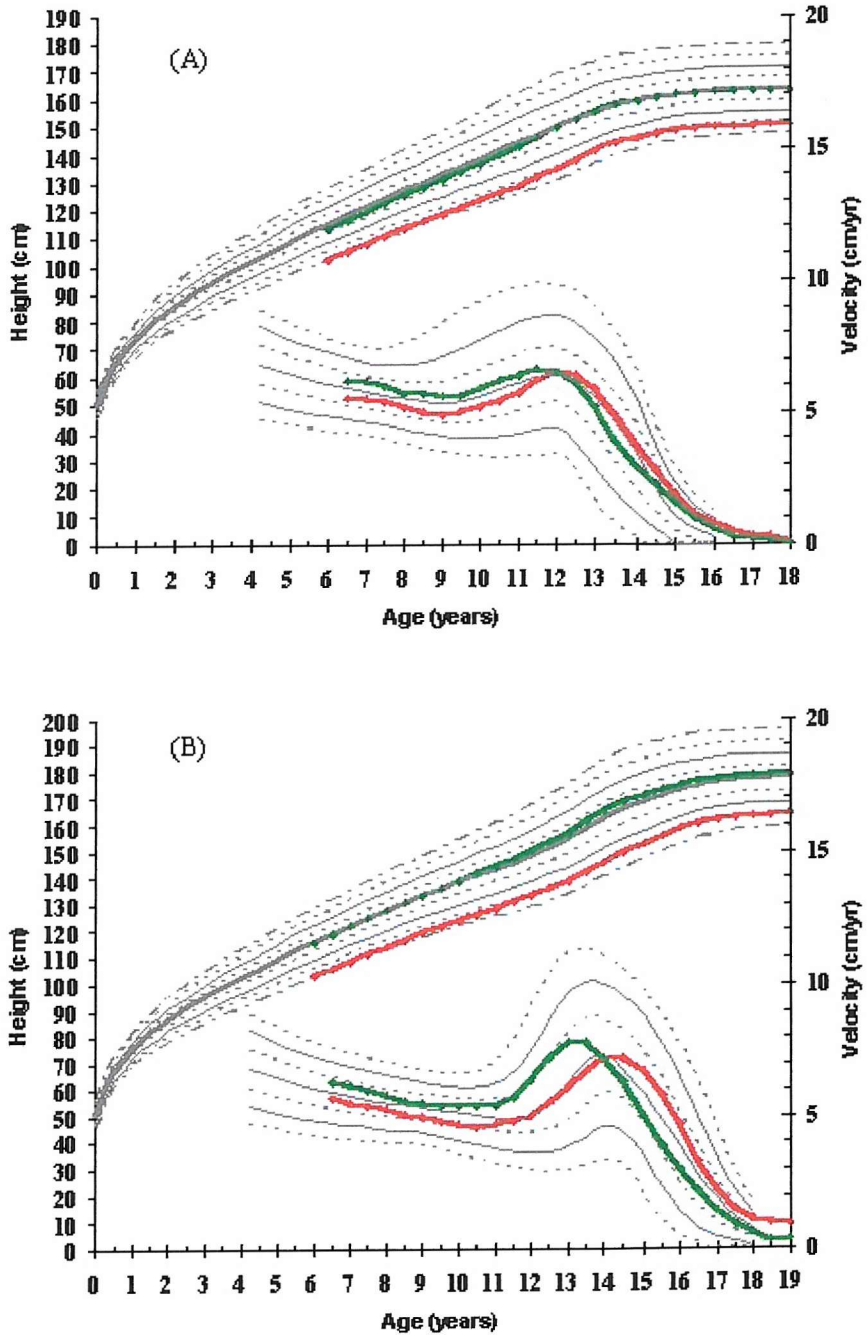


Figure 5.3 *The mean patterns of growth of height and height velocity for (a) short — and control girls —, and (b) short — and control boys —*

5.4.3 Secular trend in boys

The mean height and height velocity curves for short and control boys are shown in figure 5.3b. Once again, height has been plotted against the 1990 cross-sectional reference data [Freeman et al 1995] and height velocity against the cross-sectional whole-year velocity standards of Tanner et al (1966b). Initially, the mean height of short boys was on the 0.4th centile while that of the control boys was close to the 50th centile. The mean difference in height between the groups was 12.8cm (table 5:2b), equivalent to a final height difference of 18.4cm if the both groups continued to grow along their respective initial height centiles. During the course of the study, however, the mean height centile of both groups increased but the improvement was significantly larger for the short boys whose mean height increased by over a centile band width. As a result, the deficit in final height of short boys compared to the controls reduced to 14.5cm suggesting some degree of catch-up growth. The mean increase in height SD score for the short boys was 0.85 compared to only 0.26 for the controls *($p<0.001$)*, equivalent to an increase in final height of 5.8cm and 1.8cm, respectively. These data demonstrate a continuing secular trend in height for adult males, which is of similar magnitude to that of adult females. The overall increase in height since the construction of the 1990 UK growth reference charts corresponds to approximately 1.8cm. After adjusting for this trend, catch-up growth for short normal boys is of the order of 4 cm.

Again, as expected, the short boys gained less height during the course of the study than the control boys (table 5:2b). In contrast to the girls, however, the additional height gain of the control boys was ***not*** the result of prepubertal growth. Before puberty, the rate of growth had been greater for the control boys (see Chapter 3), which needs to be the case if a height advantage is to be maintained [Bailey 1994]. However, puberty occurred later for the short boys (see Chapter 4) and, consequently, both groups gained a similar amount between the age of 6 years and the start of the adolescent spurt (table 5:2b).

Later puberty generally results in a less intense peak [Tanner 1976] and in this sample, the mean adolescent height gain was significantly larger for the control boys (table 5:2b). Nevertheless, for both groups the pubertal spurt resulted in a height gain of over 30cm, considerably more than the 28cm reported by Tanner et al (1976) during the construction of the original growth standards. It seems that for boys, though not for girls, the continuing secular increase in height reflects at least in part a more intense period of pubertal growth.

Why such a gender difference should occur is unknown but a similar observation was observed during the construction of new growth reference standards in both the UK [Freeman et al 1995] and in the Netherlands [Fredriks et al 2000].

5.4.4 Final height compared with target height

At recruitment, the mean difference between initial and target height SD scores for the short group was -1.24 (table 3:1). Most had a height SD score below parental target with 42% having a height centile below target range (see Chapter 3, figure 3.1). On completion of stature growth, this deficit had decreased to -0.51 (table 5:1). In a review of studies investigating the adult height of short but otherwise healthy children, Ranke and Aronson (1989) noted that most attained an adult height appropriate for genetic potential. Reviewing the literature several years later, Price (1996) also observed that although mean adult height was usually below target, some regression towards parental height occurred. Both these authors concluded that this apparent improvement in final height centile, compared with parental target, was the result of catch-up growth.

However, it should be noted that in this study, no control child attained a height below target range and, as a group, the control children became relatively taller adults than their parents (table 5:1) with 62 (58%) control children attaining a final height above target. These data highlight the importance of a control group in any study and provide further evidence of the continuing secular trend in adult height. It is inappropriate to compare children with their parents without first adjusting for this trend. Interestingly, the mean difference between the height of the control children and their parents amounted to 0.27 sds, similar to the improvement in relative height for both control boys (0.26 sds) and control girls (0.32 sds) confirming the overall increase in adult height over the past 20 years is of the order of 0.8cm/decade.

Nevertheless, the increase in height centile of the short group was in fact more than could be attributed to secular trend (table 5:1), suggesting that some degree of catch-up had occurred. This in itself was not surprising. As has already been discussed, extremely short children are expected to regress towards the population mean height and therefore become relatively taller as adults. It was somewhat surprising, however, to note that the degree of catch-up appeared to be greater for the short boys (figure 5.2): the initial heights of short boys and short girls were equally extreme and that the correlation coefficient between prepubertal height and

adult height is similar for males and females [Tanner et al 1976]. Under these conditions, regression towards the mean might reasonably be expected to be similar. The data were investigated, therefore, to determine whether short normal boys experience catch-up in excess of regression towards the mean or whether short normal girls fail to achieve the expected catch-up.

5.5 Comparison of short normal boys and short normal girls

5.5.1 Regression towards the mean

Provided estimates of the population means, standard deviations and the correlation between the two measurements are known, the effect of regression on normally distributed variables measured at two distinct time points, t_1 and t_2, can be estimated mathematically [Davies 1976]. Indeed, in an investigation of prepubertal growth, Bailey (1994) has shown that the distribution of heights at t_2 for children of different heights has a mean (M_2) and variance (V_2) at t_2 which depends on their initial height such that

$$M_2 = Height_2 + sds_1 * r_{12} * sd_2 \quad \text{and} \quad V_2 = sd_2^2 (1 - r_{12}^2)$$

where,

$Height_2$ = population mean height at t_2,

sd_2 = standard deviation of population height at t_2,

r_{12} = correalation between child's height at t_1 and t_2, and

sds_1 = standard deviation score of height at t_1.

Since the correlation between heights is always <1, there is therefore a regression back to the population mean.

The correlation between prepubertal height, that is between the age of 5 and 7 years, and adult height is of the order of 0.8 [Tanner et al 1956] and growth reference data, such as the 1990 UK standards, ensure that means and standard deviations are readily available with respect to height for all ages. Consequently, using the equations of Bailey, prepubertal children whose initial height is on the 0.4th centile can be expected to have an adult height distributed somewhere between the 0.04th and 17th centiles with the mean lying close to 2nd centile. In other words, the height SD score for a child whose height is initially -2.67 sds below the mean will, on average, increase to -2.14 an improvement of 0.53 sds. This gives a

good approximation for the magnitude of the regression towards the mean for the short children in this study. Although they did not ***all*** have a height on the 0.4th centile, the mean height centile was on the 0.4th centile and all had a height below the 2nd centile.

5.5.2 Catch-up growth

There are two distinct types of catch-up growth [Boersma and Wit 1997]. Type A is the result of a sustained increase in height velocity that causes height to increase across the centile lines but which diminishes once target height for age has been reached. Two examples of this have already been documented in Chapter 3. In Type B a delay in the maturation process allows growth to continue for longer than is usual.

Figure 5.4 shows the individual change in height SD score between the age of 6 years and adult height for each short normal child. Given the shortness of their initial stature and the continuing trend towards increased height, it was not surprising that most, girls and boys, improved their height centile to some extent. The mean increase in height SD score was 0.69 but the variability was wide ranging from -1.08 to 2.24.

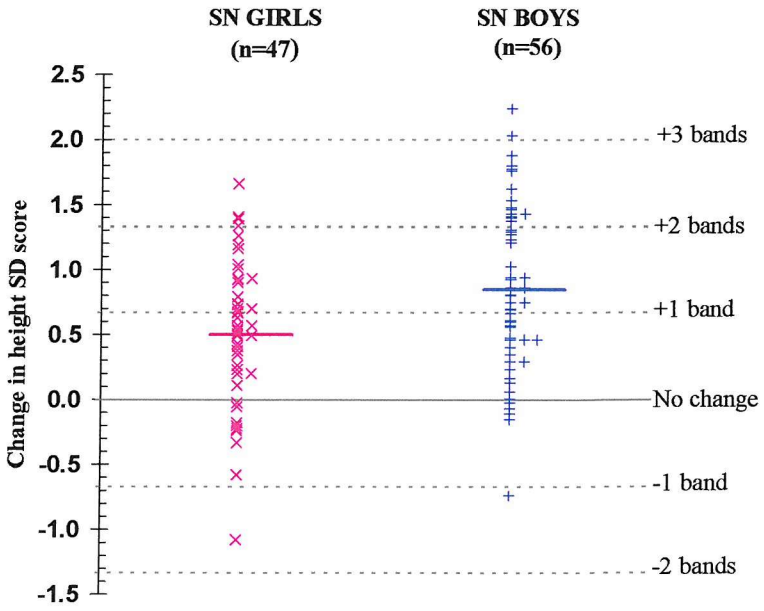


Figure 5.4 *The difference between final height SD score and initial height SD score for each short normal child*

The causes of catch-up growth

Not all short children, however, are growth retarded [Norgan 2000] and, consequently, not all will have the same potential of catch-up growth. For example, stature is largely an inherited characteristic [Tambs et al 1992] and, as a general rule, the shorter the parents, the shorter the child. On the other hand, growth failure in childhood may be the result of intrauterine conditions [Albertsson-Wikland et al 1993], poor social conditions [Dowdney et al 1987], ill-health [Prader et al 1963] or simply a slow tempo of growth [Tanner 1963].

A slowing down of the growth process is often observed in countries where malnutrition is rife [Martorell et al 1994], or where there is persistent chronic disease [Pozo and Argente 2002] but it may also occur naturally as both stature and the timing of puberty are considered to be inherited traits [Beunen 2000]. Interestingly in this study, parental target height was positively correlated, albeit weakly, with both the improvement in relative height ($r=0.27$, $p=0.007$) and the timing of puberty ($r=0.23$, $p=0.026$): short children with the tallest parents had the most catch-up and a later pubertal spurt. It is probable that at least some of the short normal children in this study simply have a slow tempo of growth as suggested by Tanner (1963).

Although many of the short normal children were small for gestation age and came from socially disadvantaged families (see Chapter 3), catch-up growth did not appear to be associated either with birth weight ($r=0.04$, $p=0.702$) or social class ($r=-0.01$, $p=0.956$). Neither of these results is surprising. Low birth weight babies do have a greater potential for catch-up but, in an investigation of the longitudinal growth of children born small for gestation age, Karlberg and Albertsson-Wikland (1995) found that unless catch-up occurred in infancy, short stature was likely to persist into adulthood. Likewise, while it is possible that some short children living in stressful social circumstances have the capacity for spontaneous catch-up growth [Skuse et al 1996], this is unlikely to be realised unless conditions for optimum growth can be restored [Norgan 1999]. In reality, most children remain in the environment that caused the retardation in the first place.

Gender differences

As mentioned previously, the mean height SD score improved for both short boys and short girls. This increase is likely to contain elements of secular trend and regression towards the

mean. Assuming that the short group experienced the same secular increase in height as the control group (0.26 sds), and that regression towards the mean was fully realised (0.53 sds), an increase in relative height of 0.79 sds might have been expected. Such an improvement was observed for the short boys but not for the short girls. There was little evidence in the present study to indicate that short boys had a greater potential for catch-up growth than the short girls. Table 5:4 shows the genetic, social and environmental profile of short boys and short girls at recruitment.

Table 5:4 *Profile at recruitment of 47 short normal girls and 56 short normal boys followed to final height*

	SHORT GIRLS		SHORT BOYS		
	Mean (SD)	**N**	**Mean (SD)**	**N**	***p-value***
Genetic profile					
Height SDS	-2.68 (0.28)	47	-2.67 (0.35)	56	0.931
Weight SDS	-2.35 (0.86)	43	-2.50 (0.77)	54	0.372
Birth weight SDS	-0.78 (1.30)	47	-0.92 (1.02)	55	0.540
Target Height SDS	-1.39 (0.70)	46	-1.51 (0.62)	54	0.376
Child SDS-Target SDS	-1.29 (0.75)	46	-1.18 (0.65)	54	0.399
Bone Age SDS	-0.68 (1.05)	38	-0.67 (0.89)	46	0.961
Birth history					
Low Birth weight (<0.4)	5 (11%)		7 (13%)		1.000
Premature (≤ 36 wks)	3 (7%)		9 (16%)		0.137
Birth Trauma	9 (21%)		13 (24%)		0.810
Maternal Smoking	17 (39%)		22 (41%)		1.000
Family environment					
Social Class					
Manual	27 (64%)		33 (73%)		0.487
Non-manual	15 (36%)		12 (27%)		
Unemployed Father	15 (34%)		6 (14%)		0.044
Nuclear Family	37 (79%)		34 (61%)		0.057
Atopic disease					
Asthma	6 (13%)		10 (18%)		0.589
Eczema	10 (21%)		12 (21%)		1.000

The genetic potential, as measured by birth weight, parental target height and bone age delay, was similar for both boys and girls. No gender differences were found in the mean height and weight centiles at entry to the study and the parents of boys and girls were equally short. At recruitment, most short children had a height SD score below parental target (see Chapter 3, figure 3.1), and boys were just as likely as girls to be identified as having non-FSS with a height SD score below target range. The birth history was comparable for boys and girls and, at recruitment, skeletal maturity was delayed by a similar amount. No major health problems were reported either at recruitment or during the course of the study and atopic disease was just as common in short normal boys as in short normal girls.

Short girls were no more likely than short boys to come from disadvantaged families although, interestingly, they were more likely to have a father who was unemployed. Unemployment is thought to be a risk factor for childhood short stature [Rona and Chinn 1991, White et al 1995], especially where this is prolonged. Even so, it is still somewhat surprising that boys are more likely than girls to achieve catch-up growth. Tanner (1989) has suggested that girls have better canalization of growth than boys and recover from growth arrest more quickly. Indeed, several authors have noted that boys seem to be more susceptible to psychosocial growth disorders [Rudolf and Hochberg 1990, Blizzard and Bulatovic 1992, Bogin et al 1992] and in a study investigating catch-up growth in infants, Albertsson-Wikland et al (1993) reported that boys appeared to be more vulnerable than girls to factors which affect catch-up growth.

Prediction of catch-up growth

Using the variables indicated in table 4:1 (see Chapter 4), stepwise multiple regression analyses were performed to determine predictors of catch-up growth for short normal children. Catch-up growth was taken as the change in height standard deviation score between the age of 6 years and final stature. For the girls, catch-up growth was more likely to occur for those with a late onset of puberty ($r=0.59$, $p<0.001$). This variable alone explained approximately one third of the variance. No other predictors were found. By contrast, two prepubertal variables, bone age delay and BMI, together explained 20% of the variance in catch-up growth for the short boys. Height centile improved most for those boys with the

largest bone age delay ($r=0.44$, $p=0.002$) and who were thinnest ($r=-0.35$, $p<0.008$) at the age of 8 years.

The lack of association between bone age and catch-up growth for the short girls was somewhat surprising. Skeletal maturation is considered to be a measure of future growth and those children with the most delay, boys and girls, are expected to show the most catch-up growth [Tanner 1989]. As discussed above, catch-up growth can be the result of a prolonged period of prepubertal growth or a sustained increased in growth velocity, which may occur at any time during the growth process, even after the pubertal spurt [Largo 1993]. Consequently, it cannot be fully assessed until after final height has been attained. Although a later adolescent spurt was associated with greater catch-up growth for short girls, bone age delay did not predict the timing or any other pubertal parameter (see Chapter 4). These data suggest that for the short normal girl a prepubertal bone age assessment is of little value. It neither predicts future growth not is it a reliable measure of the tempo of maturation.

The association between catch-up growth and BMI for short boys is also counter-intuitive. Those with the lowest BMI at the age of 8 years were most likely to experience catch-up growth. Even as a group, the short boys were thin compared to population standards with a mean BMI on the 30th centile. The increase in adult stature observed over the last 50 years in many European countries has been attributed to better nutrition, which has resulted in increased childhood stature and an earlier onset of puberty [Cole 2000]. Whilst, over-nutrition in early childhood is not beneficial to final height [He and Karlberg 2001], under-nutrition generally results in short childhood stature, delayed puberty and poor height prognosis [Rogol et al 2000].

5.5.3 The effect of catch-up growth

Table 5:5 shows the mean final height of short normal boys and girls compared with initial height, target height and predicted height. At school entry, the mean height centile was similar for boys and girls and no child had a height above the 2nd centile. Indeed, the height of 31 (55%) boys and 28 (60%) girls lay below the 0.4th centile (p=0.694). During the course of the study, most short children improved their height centile to some extent but the mean improvement was significantly greater for the boys who became relatively taller adults. Figure 5.5 shows the initial and final height SD scores for each short normal child. In this

population, three times as many girls as boys attained an adult height below the 0.4th centile (table 5:5).

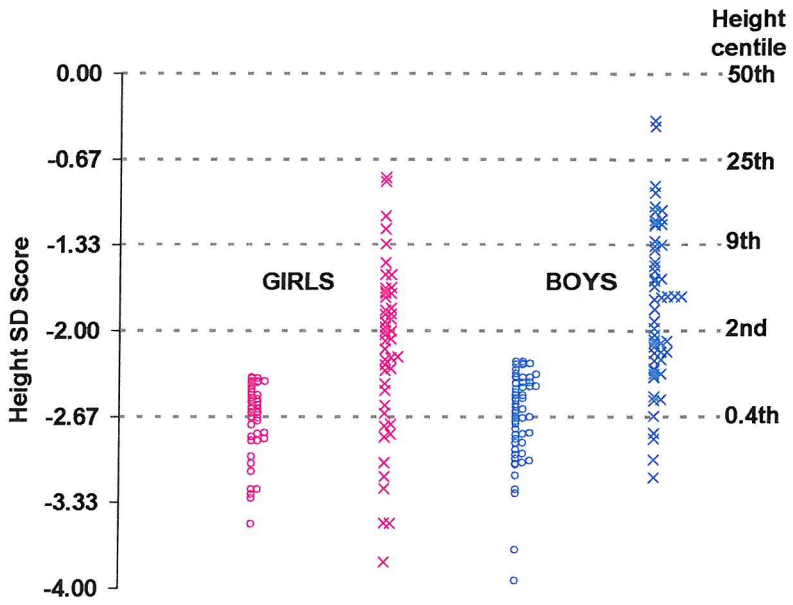


Figure 5.5 *The initial (○) and final (×) height SD scores for each SN participant*

In spite of this relative improvement in final height centile, most short children, both boys and girls, still attained a height below parental target (figure 5.6). Indeed, 82 (82%) attained a height below target height with 15 (15%) having a height below target range. Nevertheless, as adults, fewer were regarded as inappropriately short for parents although girls were more likely than boys to have heights below target range and to be considered as such (table 5:5).

Target height merely represents the average height of a large number of offspring, 95% of whom can be expected to lie somewhere within target range [Tanner 1989]. Given the selection criteria in this study, the probability that the shortest child in each family was selected is high. It is not surprising, therefore, that so many of the short children in the Wessex Growth Study fall below parental target. Indeed, these data appear to confirm previous reports. There is a consensus of opinion that short normal children, especially those with bone age delay, achieve a height below target but appropriate for their genetic potential [Volta et al 1988, Crowne et al 1990 1991, LaFranchi et al 1991, Kalckreuth et al 1991,

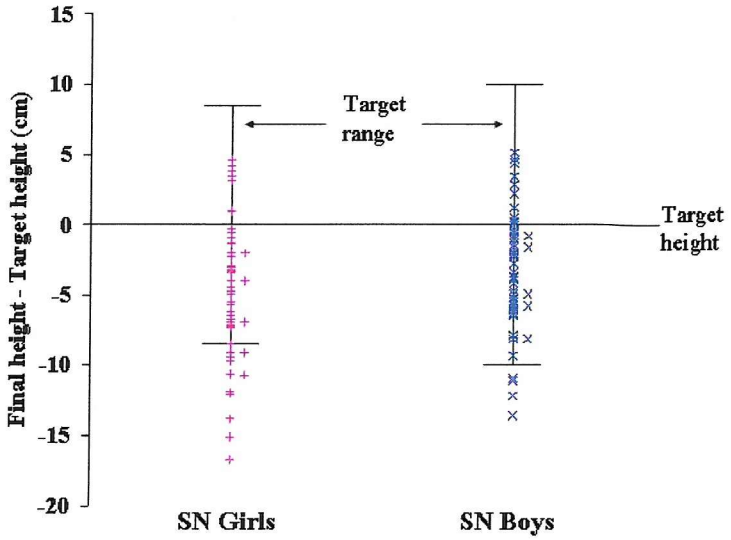


Figure 5.6 *The difference between final height and target height of 46 SN girls and 54 SN boys.*

Sperlich et al 1995]. In this study, which represents a total population of short normal children, the adult height of some 2-3% of the short normal children might, therefore, have been expected to fall below target range. However, ***three*** times as many boys and ***twelve*** times as many girls attained an adult height below target range (table 5:1). These figures are likely to be conservative as the method used to estimate target height does not allow for secular trend. In reality, these data demonstrate that many short normal prepubertal children will fail to reach their genetic potential.

5.5.4 Predicted height

Height prediction is considered to be a valuable tool of the growth specialist [Tanner et al 1983a, Preece 1988b]. First, it allows the clinician to identify the short child destined to become the short adult and second, the efficacy of growth promoting treatment can be monitored. Its usefulness, however, depends on the accuracy and reliability of the prediction [Roche et al 1975]. Skeletal maturity is considered to be a measure of the growth that has already taken place and therefore how much still remains [Tanner et al 1983] and several methods of height prediction which use childhood stature in conjunction with a bone age assessment are commonly used in clinical practice [Preece 1988]. Most have been validated on groups of normal children followed to final height and, strictly speaking, should not be

applied to children exhibiting abnormal patterns of growth [Roche 1984]. The TW-II method, however, has been developed using a sample that includes very tall and very short children [Tanner et al 1983a]. In this study, adult height was estimated using this method for those short normal children whose bone age was assessed shortly after recruitment (mean age 5.75 years). Figure 5.7 shows the difference between final height and predicted height for each of these children followed to final height.

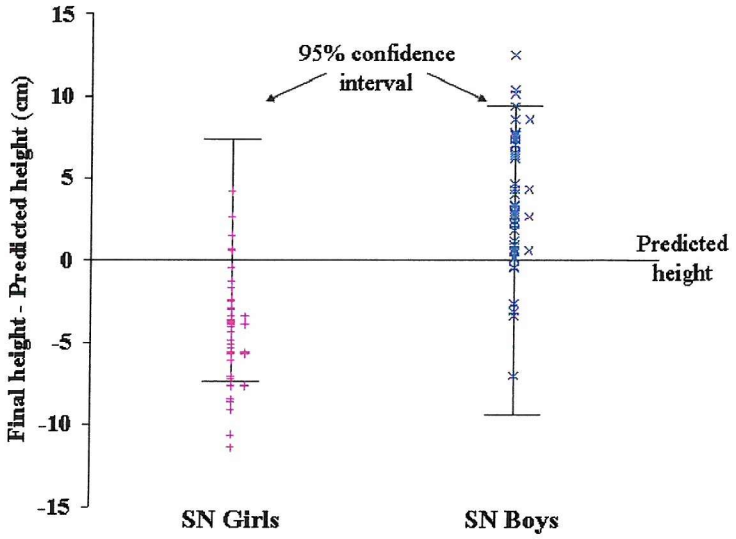


Figure 5.7 *The difference between final height and predicted height of 46 SN boys and 38 SN girls.*

Compared with short boys, short girls had similar initial heights and bone age delays. Nevertheless, short girls were expected to achieve greater catch-up growth and become relatively taller adults (table 5:5). Their mean height was predicted to increase to the 5th centile while short boys were predicted to remain below the 1st centile. In fact, a reversal of this prediction occurred. As a result, 33 (87%) girls but only 6 (13%) boys failed to reach their predicted height *($p<=0.001$)*.

This finding was somewhat surprising. Those studies, cited earlier, that have examined the final height in short but otherwise healthy children have concluded that most reach a height close to prediction. The method of prediction varies from study to study but Bramswig et al (1990) and Sperlich et al (1995) compared the available methods and found that mean final

height generally equalled or exceeded the mean predicted height, regardless of the method used. Unlike the children in the present study, however, these data generally concern children, mainly boys, diagnosed with CDGP who come to the attention of the paediatrician typically around the age of 12 to 14 years [Price 1996]. It should also be remembered that in a clinical setting height predictions are not made for groups but for individuals and all of the available methods, including the TW-II method, produce estimates with fairly broad error limits [Hintz 2001].

Table 5:5 *The mean (SD) final height of 56 SN boys and 47 SN girls compared with initial height, target height and predicted height*

	BOYS	**GIRLS**	*p-value*
Final height			
Final height (cm)	164.6 (4.4)	150.5 (4.1)	*<0.001*
Final height SD score	-1.81 (0.62)	-2.14 (0.67)	*0.012*
Number(%) <0.4th centile	4 (7%)	10 (21%)	*0.046*
Comparison with initial height			
Initial height SD score	-2.67 (0.35)	-2.68 (0.28)	*0.931*
Catch-up growth ΔHSDS	0.85 (0.63)	0.50 (0.58)	*0.005*
Comparison with target height			
Target height (cm)	167.9 (4.3)	155.4 (4.2)	*<0.001*
Target height SD score	-1.51 (0.62)	-1.39 (0.79)	*0.376*
Final-target height (cm)	-3.4 (4.2)	-4.9 (5.2)	*0.108*
Number (%) below target range	4 (7%)	11 (24%)	*0.026*
Comparison with predicted height			
Predicted height (cm)	160.9 (2.5)	154.5 (1.6)	*<0.001*
Predicted height SD score	-2.54 (0.37)	-1.55 (0.26)	*<0.001*
Final-predicted height (cm)	3.9 (4.2)	-4.2 (3.5)	*<0.001*

Preece (1988b) investigated the source of the prediction errors and concluded that the age and magnitude of PHV had significant effects but that bone age in younger children could ***not*** predict either the time or intensity of the pubertal spurt. Others have also questioned the ability of prepubertal bone ages to predict future growth and development [Roche 1984, Ranke 1996]. Preece also found that under-prediction was more likely for the later maturing

child, particularly if the growth spurt was greater than expected. Compared to the control children, the adolescent spurt tended to be later for the short boys but not for the short girls and, in spite of the later peak, the magnitude of the peak was comparable for short and control boys (see Chapter 4). Short boys might therefore have been expected to reach an adult height above that predicted. However, given the secular trend in height observed for both males and females in this population, the over-prediction for short girls was somewhat surprising.

The data from this study also demonstrate the futility of adult height prediction of prepubertal children in a clinical setting. At best it is insensitive and at worst misleading. The TW-II height prediction method could not predict with any degree of certainty which children would become very short adults, that is with a height below the 0.4^{th} centile. Although 32 (9 girls) children were predicted to become very short adults, only 14 (4 boys) children actually attained a height $<0.4^{th}$ centile and only 4 (3 boys) of these children were correctly identified. Such a result is no more than a chance agreement (*Kappa -0.019*).

5.5.5 The pattern of growth

There is little difference in the heights of prepubertal boys and girls but, as adults, men are, on average, approximately 14cm taller than women. The adolescent spurt, which occurs later in males and is more intense, is largely responsible for this difference [Tanner 1962]. In a longitudinal analysis investigating the growth of 55 boys and 35 girls, Tanner et al (1976) found that the gender difference in stature was due more to the difference in timing of the spurt rather than the adolescent height gain. Buckler (1990) confirmed this finding in a later study investigating the growth characteristics of children in the North of England. On the other hand, Largo et al (1978), using a larger sample of 222 (112 boys) children, estimated that the greater male spurt accounted for almost one half of the gender difference.

In the present study, the heights of the short boys and girls were similar at recruitment but the mean gender difference in their adult heights was 14.1cm. Table 5:6 shows the mean pattern of growth from the age of 6 years for those boys and girls followed to final height. Most of this difference in adult height was the result of the longer period of pre-pubertal growth allowing boys to increase their height by, on average, 9.85 cm more than girls ($p<0.001$). Nevertheless, the greater intensity of the male pubertal spurt also contributed significantly

Table 5:6 *The pattern of growth from age 6 years to final height for 56 SN boys and 47 SN girls*

	BOYS	GIRLS	Difference	*p-value*
At age 6 yrs				
Height (cm)	103.0 (1.8)	102.5 (1.3)	0.5	*0.129*
At pubertal take-off				
Age (years)	11.75 (1.17)	9.76 (1.07)	1.99	*<0.001*
Height (cm)	132.1 (6.3)	121.7 (4.9)	10.4	*<0.001*
At peak height velocity				
Age (years)	14.49 (0.96)	12.25 (0.94)	2.24	*<0.001*
Magnitude of PHV	9.58 (1.33)	8.09 (0.87)	1.49	*<0.001*
At completion of spurt				
Age (years)	16.79 (0.94)	14.42 (0.92)	2.38	*<0.001*
Height (cm)	162.4 (4.4)	148.2 (4.1)	14.2	*<0.001*
At final height				
Height (cm)	164.6 (4.4)	150.5 (4.1)	14.1	*<0.001*

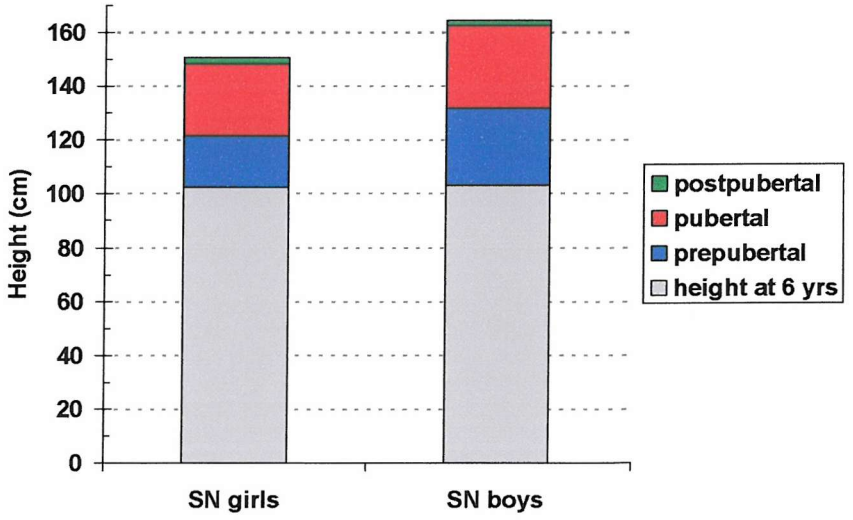


Figure 5.8 *Mean contribution to adult stature from each phase of growth for 47 short normal girls and 56 short normal boys*

adding a further 3.96cm to the difference accrued before puberty ($p<0.001$). Figure 5.8 illustrates the effect of these increases.

It is possible, that this gender difference in adult height between the short boys and short girls will increase. As discussed earlier, it is difficult to determine the precise age when stature growth ceases but boys do continue to grow for longer than girls and several authors have noted significant height gains for some boys after the age of 18 years, especially where puberty is delayed [Hulanicka and Kotlarz 1983, Hagg and Taranger 1991]. Using curve fitting techniques, Roche and Davila (1972) have estimated the median age at final height to be 21.2 years for boys and 17.3 years for girls. In this study, the median age at the last recorded measurement was 19.2 years and 18.57 years for boys and girls, respectively. Pubertal growth contributed significantly to final height for both short boys and short girls. On average, 19% of adult height in both sexes was due to the adolescent spurt, but the range was wide (10% to 28%). The mean gain was higher than the 16% reported by Tanner et al (1976) using the growth data of children born in the 1950's. However, the increase in height during adolescence was comparable for short and control girls (*SN: 28.8 (4.3)cm , C: 28.2 (6.2)cm, $p=0.580$*) and for short and control boys (*SN: 32.5 (5.2)cm , C: 34.4 (5.7)cm, $p=0.057$*). Consequently, given the shortness of their stature at the start of the spurt, pubertal growth might have been expected to make a bigger contribution to adult stature of the short group. Nevertheless, even for the controls the amount gained in height during the pubertal spurt was equivalent to 18% of final stature. This may simply reflect differences in the age at final measurement. In Tanner's sample, final height was considered to have occurred once height velocity had reduced to <1cm/yr. It is unclear for how much longer these children were measured but growth can continue to increase for some time after this point [Roche and Davila 1972]. Alternatively, this difference may indicate that the overall increase in adult stature since the 1950's is indeed the result of more intense pubertal growth as has been suggested [de Muinich Keizer and Mul 2001].

Prepubertal growth of low intensity is generally followed by a more intense period of pubertal growth [Tanner et al 1976, Luo and Karlberg 2000, Vizmanos et al 2001] and in this study, the compensatory nature of pubertal growth was apparent for both short girls and short boys. The relation between the gain in height from the age of 6 years until the start of the spurt and the adolescent height gain is shown in figure 5.9. The correlation coefficient

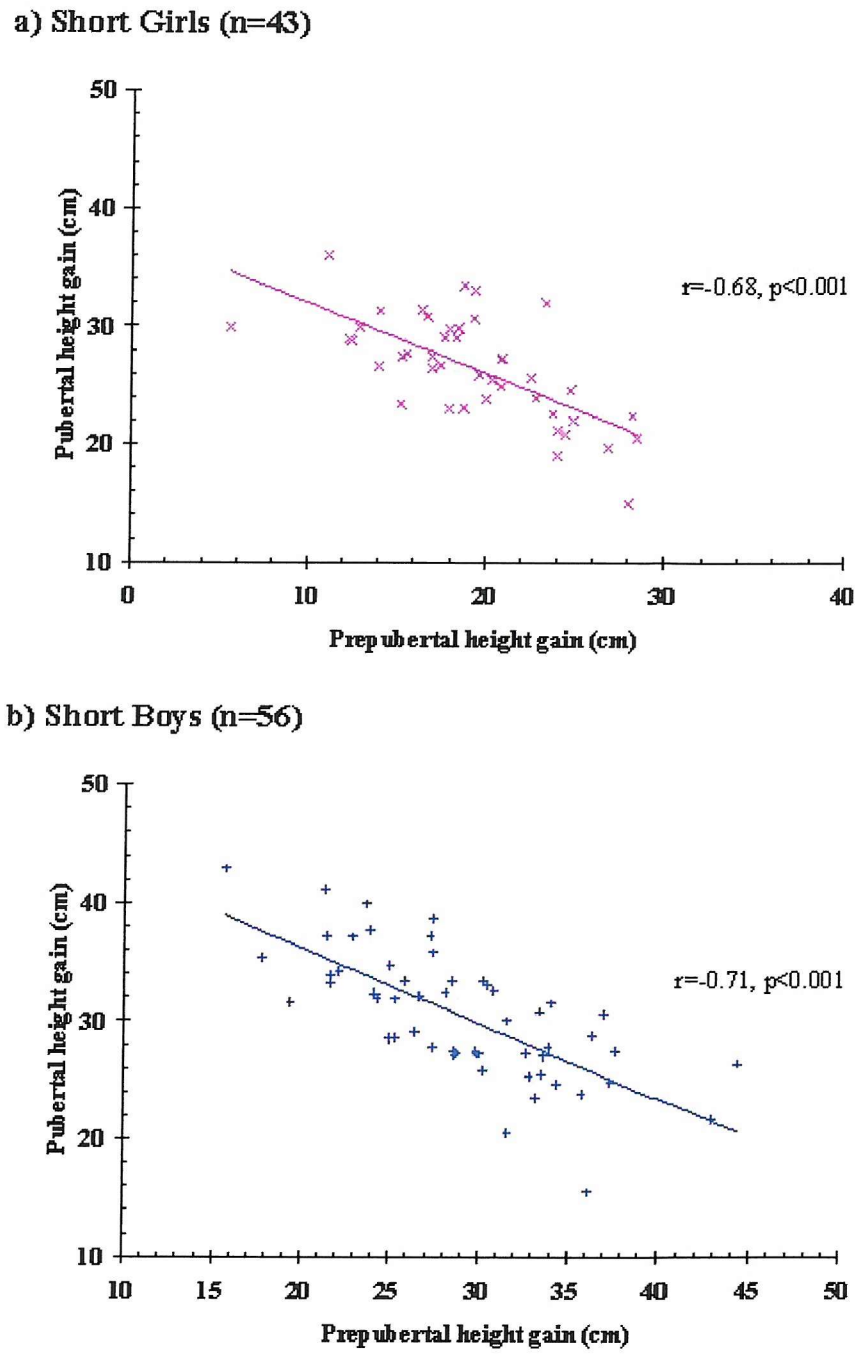


Figure 5.9 *The relation between prepubertal and pubertal height gain for a) short normal girls and b) short normal boys*

between these two variables was -0.68 and -0.71 for girls and boys, respectively. These data demonstrate the variability of the growth pathway and confirm the difficulty of predicting adult height from childhood height. There are evidently numerous ways to achieve identical adult size and no phase is more important than another. Indeed, it has been demonstrated that adult shortness is the result of more than one phase of poor growth [Luo and Karlberg 2000]. It might therefore be expected that pubertal growth would be particularly important in defining the adult height of the short normal prepubertal child who, by definition, has already demonstrated less than optimum growth.

Interestingly, the contribution of the adolescent height spurt, defined by the age at PHV, the magnitude of PHV and the duration of the spurt, determined adult height to a greater degree for short girls than for short boys. In a regression analysis, these three pubertal parameters explained 41% of the variance in adult height for the girls but only 15% for boys. In a recent publication, Sheehy et al (2000) made a similar observation though the reason for this is unclear.

5.6 Factors influencing final height

In a total population study involving over 74,000 adults, Tambs et al (1992) demonstrated the strength of genetic transmission of height. The strong family resemblance between the adult height of family members increases as the family relationship becomes closer. These authors also noted, however, that the correlations between parents and offspring from different generations were subject to change and suggested that this was the result of an interaction effect between genes and the environment. Two longitudinal studies, again using large population samples, support this hypothesis. In a follow-up of a national cohort from birth to adulthood, Kuh and Wadsworth (1989) found that environmental factors in childhood influenced adult height even after adjustment for parental height and birth weight. A social class gradient in height was apparent but birth order, family size and overcrowding were also found to be independent predictors of adult height. More specifically, in an investigation of living conditions in Sweden, short adult stature, defined as being shorter than 1 SD below the mean, was found to be a reflection of 'adverse' conditions in childhood [Peck and Lundberg 1995]. These adverse conditions consisted of not only economic hardship but also a stressful family environment. Nevertheless, studies, such as these, which measure the variables that affect the heights of all members in a society may not be applicable to the very short child.

As Parkin (1989) has pointed out, "*important but special influences affecting the few may be hidden by the common but less relevant influences affecting the majority*".

As well as measuring height and weight, a great deal of background information was collected for each short normal child in this study. This information, which includes parental heights, birth history, social & family background, and medical history, provides the opportunity to examine the associations between adult stature of the short normal child and these social and biological influences. Regression analyses were performed using the variables indicated in table 4:2 (see Chapter 4). In view of the significant gender differences in adult height, boys and girls were examined separately. The results are shown in table 5:7.

Table 5:7 *Results of a stepwise regression to find predictors of final adult height of short normal children*

Step	Variable	R^2	Change in R^2	F Ratio	*p-value*
Short girls					
1	Age at PHV	0.29	-	13.32	0.001
Short boys					
1	Target height	0.27	-	15.68	<0.001

In a stepwise multiple regression analysis, the only predictor of final height for the short girls was the age at PHV, which accounted for 29% of the variance. Figure 5.10 shows the relation between final height and the timing of puberty for the short children. A positive correlation was found for short girls ($r=0.54$, $p<0.001$) and for short boys ($r=0.34$, $p=0.010$). Those with later puberty became the taller adults. These data appear contrary to other reports, which indicate no relationship between adult stature and the timing of the adolescent growth spurt [Tanner et al 1976, Hulanicka and Kotlarz 1983, Abbassi 1998, Vizmanos et al 2001]. However, the timing of puberty is associated with childhood height such that the pubertal spurt tends to occur earlier in children who are taller [Tanner et al 1976, Tanaka et al 1988]. Thus, within the population at large, any reduction in adolescent height gain as a result of earlier maturation tends to be compensated by enhanced prepubertal growth. Tanaka et al (1988) have demonstrated that after correcting for prepubertal height, the timing of puberty

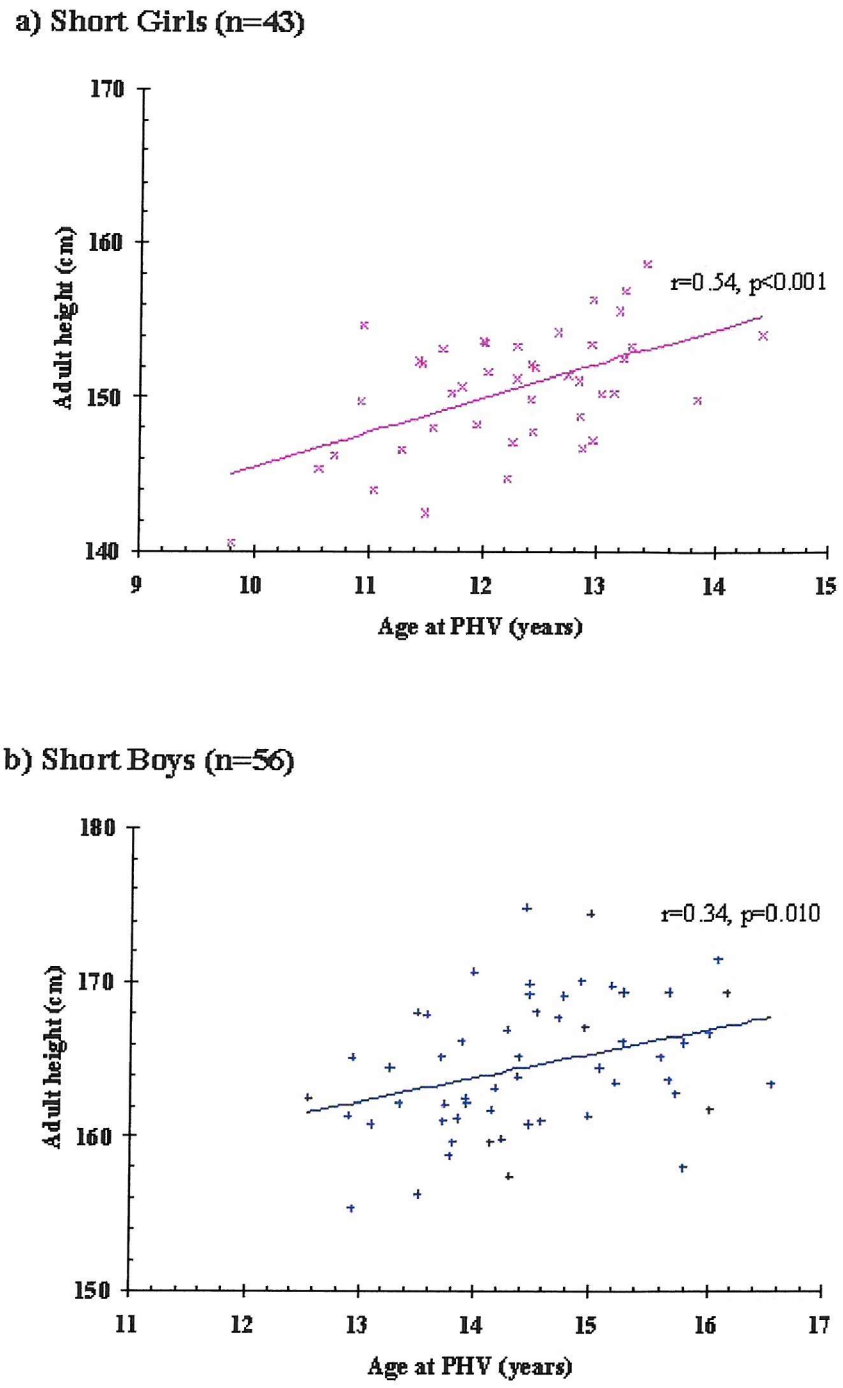


Figure 5.10 *The relation between age at PHV and adult height for a) short normal girls and b) short normal boys*

correlated positively with final height, confirming that for the short normal child a delay in maturation is advantageous to adult stature.

A similar amount of the variance in the adult height of short boys was also explained but this time the predictor was parental target height. Both the timing of puberty and parental target height have a strong genetic component. Interestingly, for short boys there was an association between parental target height and the age at PHV ($r=0.28$, $p=0.041$): those with a slower tempo of growth tended to have the taller parents. Constitutional delay in growth and puberty is often familial [Duck 1996]. It is characterised by a slower than normal growth and pubertal development rate but eventual adult height is within genetic potential [Ferrandez Longas et al 1996]. Compared with Tanner's standards and with the control boys, the short boys in this study were more likely to have delayed pubertal growth and to achieve a height within target range. It would seem genetic transmission of both adult stature and the tempo of maturation is likely for short normal boys.

The genetic control of the tempo of maturation is not necessarily dependent on the genetic control of adult stature [Tanner 1989] and for the short girls no association was found between the timing of puberty and parental target height. Indeed, parental height had very little effect on the height outcome of short girls, explaining less than 5% of the variance. Short girls were also more likely than short boys to attain a height below target range (table 5:5). A possible explanation for these findings is that in early maturing girls the adolescent height gain does not fully compensate for the shortened period of growth. Investigating the interactions of the tempo of maturation, parental height and stature of adolescent boys and girls, Koziel (2001) found that, while midparental height influenced the timing of the spurt, it had no effect on the intensity of the peak, especially for girls. Indeed, in the present study it has already been observed (see Chapter 4) that early maturation in short normal children was not accompanied by a higher compensatory peak (figures 4.7, 4.17) and that short normal girls were not likely to experience pubertal delay.

Stepwise regression analysis did not reveal any social or environmental predictors of final height for either short girls or short boys. It should not be concluded, however, that these factors have no influence on childhood growth. Genetic variables explained less than 30% of the variance in the adult stature of short normal children. Economic hardship, emotional deprivation, and physical and sexual abuse can result in growth failure [Leung et al 1993].

Nevertheless, not all children react to stress in the same manner [Skuse et al 1996]. Indeed, as Tanner (1989) has pointed out, each child is an individual and for optimal development everyone should have a different environment.

5.7 Clinical Implications

Short stature is a good index of organic disease [Voss et al 1992] and in some conditions, such as GHD and Turner syndrome, it may be the only presenting symptom [Hyer et al 1995]. These conditions benefit from early diagnosis and treatment and consequently, community height screening at school entry has been recommended [Hall 2000]. Such a procedure, however, is likely to identify many short normal children raising concern among parents and alerting them to the possibility of growth hormone treatment. The data presented here suggest that in relation to their peers, a substantial number of short normal children will remain short and fail to reach their genetic potential.

Short stature is often present in many pathological conditions, but it is not in itself a disease [Taback et al 2002] nor is it life threatening. Consequently, once a short child is referred *regardless* of the underlying cause [Bolt and Mull 2001], the decision to reassure or treat with growth-promoting agents requires knowledge of potential outcome resulting from both treatment and non-treatment [Price 1996]. Final height is one aspect and where there is clear pathology, the clinician can be confident that without the appropriate intervention, adult height will be compromised. Other considerations, however, include the future health and well-being of the child. Many disorders of growth also result in a variety of physiological disturbances [Smith 1967] and psychological dysfunction [Skuse 1987]. For example, growth hormone has major metabolic actions, which are important for bone mineralization, body composition and cardiac function. Consequently, growth hormone deficiency (GHD) not only affects the growth of children but also results in an increased risk of osteoporosis and cardiovascular disease in later life [Murray and Shalet 2000]. Osteoporosis is also a common complication in women with Turner syndrome and initial studies indicate that growth promoting treatment during childhood may prevent bone fractures in the future [Landin-Wilhelmsem et al 1999].

Ethically, treatment decisions for the short normal child should be made using the same criteria but the potential outcomes are less clear. Using referred samples, several authors have

reported that short stature, even if this is not associated with pathology, is detrimental to academic achievement and psychosocial functioning [Stabler et al 1990, Allen et al 1993, Sandberg et al 1994, Skuse et al 1994a]. The Wessex Growth Study, however, has demonstrated that among the normal population those who are short as children, adolescents or young adults are no more likely to be disadvantaged socially or psychologically than those who are taller [Voss et al 1991a, Voss and Mulligan 1994, Downie et al 1997, Ulph et al in press]. Recent research does suggest that short normal adults have greater cardiovascular risk [Parker et al 1998, Forsen et al 2000] but an association between body height and health is not proof of causation [Silventoinen et al 1999]: biological and social factors evolve together influencing both adult stature and health outcome [Barker et al 2001]. More research is needed to assess the health risks of short normal stature but recognising which children might benefit from intervention is likely to require a multi-professional team involving among others the growth specialist, social worker and psychologist.

5.8 Summary

This study has followed the growth and development of an unselected population of short normal children from school entry until final height together with controls of 'average' height. The mean height centile of both groups improved suggesting a continuing secular trend in adult stature within the UK. The increase in relative height was greater for the short children implying some degree of catch-up growth. Some short children have become taller adults than others but in relation to their peers, a substantial number have remained short and failed to reach their genetic potential. Few variables, genetic or environmental, were found to be predictors of the adult height of short normal children and much of the variance is unexplained.

Data from this study have also revealed an important gender difference in the patterns of growth of short normal children which may have relevance to their clinical management. Although short boys and girls have similar genetic backgrounds, only short boys are likely to experience pubertal delay. Consequently, catch-up growth was significantly greater for the short boys and girls were ***three*** times more likely than boys were to become very short adults with a height below target range.

The data presented here have also demonstrated that adult height prediction based on childhood height and prepubertal bone age cannot reliably predict adult height or identify

those who will become very short adults. Nor is continued monitoring likely to improve the success rate: prepubertal height gain is negatively correlated with pubertal height gain and any apparent 'catch-up' growth in the prepubertal years may well be compromised by a poor pubertal spurt. This study has demonstrated the individuality of the growth pathway, which is influenced by many different factors. Recognising which children might benefit from intervention requires a multi-professional team including the growth specialist, social worker and psychologist.

Chapter 6: SUMMARY AND CONCLUSIONS

"The Child is father of the Man"
Wordsworth 1902

Many pathological conditions affect childhood growth and in some cases, short stature may be the only presenting symptom [Hyer et al 1995]. Not all growth-related disease is remediable but for some conditions, such as GHD, coeliac disease, Turner's syndrome and hypothyroidism, early detection and treatment improves the prognosis for final height. Many experts also believe that school entry offers a unique opportunity to screen the whole population and produce an acceptable yield of previously undiagnosed pathology [Hall 2000]. Such a programme, however, would undoubtedly identify an even larger number of short but otherwise healthy children raising concerns among parents and alerting them to the possibility of growth promoting treatment. Not all very short children, however, will become very short adults and when counselling parents the clinician must be able to provide an informed prognosis concerning the child's likely adult height.

Data from this study have clearly shown that adult height prediction based on prepubertal height and bone age cannot reliably predict the adult height of short normal children or identify those children destined to become very short adults. Others have confirmed the failure of height prediction methods to provide accurate estimations of adult height [Preece 1988, Sperlich et al 1995, Price 1986, Hintz 2001]. Indeed, Hintz has suggested abandoning height prediction for individuals in favour of group data to determine relative risk of significant short stature.

The Wessex Growth Study is the first study to monitor a group of short normal children until final height allowing the risk of short adult stature to be assessed. Moreover, the children were identified as a result of routine height screening at school entry and therefore are typical of the false positives that would be produced if, as proposed [Hall 2000], such a programme is introduced. At school entry, the short normal child is characterised by a relatively low birth weight, short parents and a delayed bone age. Many appear to be inappropriately short for parents with a height centile below target range. During the course of the study, the mean height centile of both short boys and short girls improved and as adults, fewer were considered to be short for parents. These data seem to confirm previous reports that short

normal children in the main achieve spontaneous catch-up growth and become relatively taller adults [Ranke and Aronson 1989, Price 1996]. ***However***, this study has the advantage of an age- and gender-matched control group of 'average' height and an improvement in height centile was also observed for this group. The control children therefore became relatively taller adults than their parents confirming that adult stature in the UK is continuing to increase.

These data highlight the importance of a control group in any study. This is perhaps even more important in a longitudinal study of growth. The interpretation of growth data requires relevant population standards, which should be updated every 10-20 years, depending on the population secular trend [GH Research Society 2000]. Studies investigating the final height of short but otherwise healthy children generally span more than a decade. The present study is the only study to incorporate a control group of average height children allowing any overall increase in adult stature to be estimated. These data show that for both males and females the secular trend in adult height since the construction of the latest standards is of the order of 1.8cm.

Nevertheless, the increase in relative height was greater than this for the short children implying some degree of catch-up growth, particularly for short normal boys. Indeed, the data from this study have revealed important gender differences in the patterns of growth of short normal and control children which may have relevance for the clinical management of short normal children.

First, although both short normal boys and girls have similar genetic backgrounds, only short normal boys are likely to experience pubertal delay. For the short girls in this study, the timing, magnitude and duration of the pubertal spurt were comparable to Tanner's original standards compiled 30 years previously. The mean values for age and magnitude of PHV and age at menarche were also close to Tanner's 50^{th} centile values. On the other hand, even though short normal boys had similar birth weights, skeletal delay and were just as likely as short normal girls to be short for parents, their pubertal spurt occurred, on average, some six months later than expected. As a result of this delay in pubertal onset, catch-up growth was significantly greater for the short normal boys and consequently, short normal girls were ***three*** times more likely than boys were to become very short adults with a height below target range. Adult height was below the 0.4^{th} centile for 21% of girls compared with 7% of

boys, and below target range for 24% of girls and 7% of boys instead of the expected 2-3%. It should also be remembered that these figures are based on apparently outdated standards, which take no account of secular trend. In reality, this study has demonstrated that many short normal prepubertal children, particularly girls, will remain short as adults and fail to reach their genetic potential.

Group differences were also apparent for the boys but not for the girls in the study. Short and control girls had very similar patterns of growth. Before puberty, the mean growth of both groups stayed close to their initial mean height centile lines. The pubertal spurt of short normal girls mirrored that of the taller control girls. There were no discernible differences in the timing or duration of puberty and the adolescent height gain was also similar. In contrast, short boys were more likely than their controls to have a delayed onset of puberty followed by a less intense adolescent spurt.

Constitutional delay of growth and puberty is a condition that is considered to warrant treatment [Stanhope et al 1985, Crowne et al 1990, Albanese and Stanhope 1995]. It is diagnosed when pubertal development occurs more than 2 years after the mean chronological age for the onset of puberty. Boys are referred more commonly than girls though it is uncertain whether this is arises from a genuine gender difference in the incidence or whether the psychosocial consequences of the condition have a greater effect on boys, making them more likely to receive medical attention [Burstein and Rosenfield 1987]. The data from this study indicate the former. It was possible only to assess puberty retrospectively using the height velocity curve but a significant delay in the adolescent spurt was observed for 1 in 10 boys instead of the expected 2%. By contrast, most girls experienced puberty within the expected age range. Interestingly, the taller control boys were just as likely to experience significant pubertal delay as those who were short and in all cases this delay was preceded by a transient fall in height centile. This may explain why previous research investigating the final height of short normal children has concluded that most achieve a satisfactory height.

Clinical implications

The statistical likelihood of significant short stature or pubertal delay may aid clinical decisions but it is not helpful to the individual child. Inevitably, some of the children in this study did improve their height but many remained short with respect to their peers and genetic expectations. This raises several questions. First, *does short stature matter?*

Data from the Wessex Growth Study would suggest that for the short normal child the answer is no. Short normal children have no pathological condition and are no more likely than those who are taller to suffer any psychological disadvantage [Voss et al 1991a, Voss and Mulligan 1994, Downie et al 1997]. The paediatrician, however, must respond to the needs of the individual child and is concerned not only with the present but also the long-term consequences and for the short normal adult, the outcome in terms of psychological health and morbidity is less certain. Short adults are commonly considered to be psychosocially disadvantaged [Macintyre 1988, Zimet et al 1997] while several studies have linked short adult stature with increased risk of hypertension, cardiovascular disease, stroke and diabetes [Parker et al 1998, Forsen et al 2000, Langenberg et al 2003, Lawlor et al 2002]. Poor childhood growth is also reported to contribute to osteoporotic fracture in later life [Javaid and Cooper 2002]. Low birth weight and deprived living conditions exacerbate these risks [Bosma et al 1999, Barker et al 2001]. At the time of recruitment to this study, the short children by definition had already exhibited less than optimum growth and typically were of low birth weight and from low socio-economic class. Early intervention may well improve the future well-being of these children, which leads to the second question; *what can be done about it?*

There is evidence from the Wessex Growth Study to suggest that growth hormone (GH) therapy started in early to mid-childhood may improve the height outcome, at least for girls [McCaughey et al 1998]. The first randomised controlled trial to monitor a group of short normal girls until final height reported that GH treatment led to a mean increase in final height of approximately 6cm compared with equally short, age-matched controls. This increase is equivalent to the increase observed for girls with Turner syndrome treated from a similar age and for a similar duration [Betts et al 1999]. Nevertheless, whether such an increase in final height will result in improved well-being or life expectancy is unknown. Inequalities in the health of children and adults are considered to be the result of poor social conditions during childhood [Carter 2002]. It is possible that increased involvement of health professionals prenatally and in early childhood may more effectively produce an improvement in birth weight, childhood growth and consequently adult height and well-being. Alternatively, it may be more appropriate to wait to for the emergence of symptoms, physiological or psychological, and treat accordingly. This is an area that requires further

research but whatever intervention is deemed most appropriate it should be aimed at those most likely to benefit, leading to a third question; *which children will become short adults?*

It is recognised that growth throughout childhood is a "continuous and complex interaction of heredity and environment" [Tanner 1989]. A primary aim of this thesis was to assess the impact of these factors on the pattern of growth and final height outcome. A summary of the main findings is shown figure 6.1.

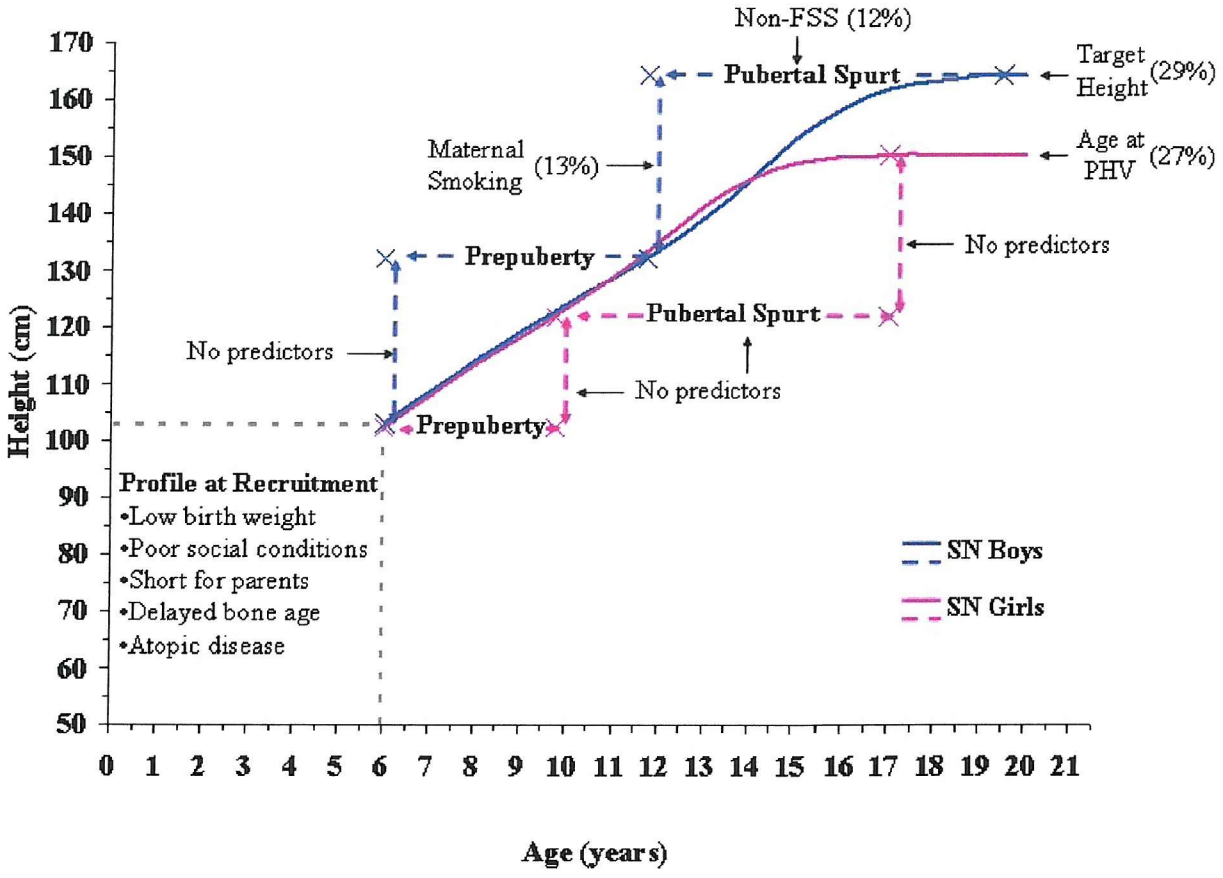


Figure 6.1 *The mean growth pattern of short normal children from recruitment at school entry to final height. Predictors of prepubertal and pubertal height gains, the timing of puberty and final height are shown with the amount of variance explained.*

No variable, genetic or environmental, predicted height gain either in the prepubertal or pubertal phase of growth for short normal girls but maternal smoking during pregnancy was a predictor of pubertal height gain for short normal boys. Surprisingly, those boys whose

mothers smoked had the higher pubertal height gain. Boys with the tallest parents, who were therefore shortest for parents at recruitment, tended to have a delayed pubertal spurt and become the tallest adults. Likewise, girls with later puberty tended to become the taller adults. None of the variables examined in this thesis, however, could predict the timing of puberty for girls. Much of the variance in the adult height of short normal children is unexplained. The data presented in this thesis has also shown that continued monitoring is unlikely to improve the success rate. Indeed, prepubertal height gain correlates negatively with pubertal height gain such that any apparent 'catch-up' growth in the prepubertal years was often compromised by a poor pubertal spurt. It should not be concluded, however, that adult risk of ill-health cannot be identified from childhood growth. As a community based study incorporating a total population of short normal children, the Wessex Growth Study has many advantages over previous research investigating short stature. Nevertheless, there are several limitations.

First, this study primarily investigated stature growth and few measures of nutritional status were available. Good nutrition, however, is essential for normal growth and development. This is particularly so during puberty, which is marked by rapid changes in body size, shape and composition [Rogol et al 2000]. It is of interest to note that in this study, stepwise regression analyses found the only predictors of final height to be the timing of puberty for girls and parental target height for boys. However, for the short boys target height and the timing of puberty were interrelated such that for boys as well as girls those with later puberty tended to become the taller adults (see figure 5.10). None of the variables measured in this study were found to be reliable predictors of the timing of puberty. It is possible that more direct measures of body fat, fat distribution and body proportions would have yielded stronger predictors.

Second, although height is an indication of social and nutritional status as well as genetic potential, it also reflects far more subtle influences, such as emotional and psychological well-being. Genetic and environmental factors tend to persist throughout childhood [Norgan 2000] but psychological trauma may be transient and results from various sources, such as family conflict, school or peer pressure. Even so, insults of this nature can have lasting effects [Peck and Lundberg 1995, Montgomery et al 1997], but they are difficult to measure and to quantify. In the present study no robust measure was available to quantify or monitor

emotional well-being and it may be that those children who remained short as adults were those most likely to have experienced emotional conflict.

Third, it should be noted that at recruitment to the Wessex Growth Study, the children were already 5 to 6 years old and almost half were considered to have non-FSS suggesting a period of poor growth had already occurred. Foetal growth and growth during infancy are considered crucial for subsequent long-term growth [Buckler 1994]. Many experts believe that adverse influences in the first few years of life are not fully reversible. In the present study, few measures were available to evaluate growth in these periods. Prenatal growth was assessed using birth weight, a crude summary index of growth, while the only measure of pre-school growth was the discrepancy between child and parental target height. This, however, may not be a useful marker as parents themselves may have failed to reach their own genetic potential. It is possible that continuous monitoring from birth would identify those likely to benefit from intervention. At the time of this study, it was not possible to obtain retrospective height and weight measurements prior to school entry as no central database of early growth data was available and parent-held records were not in common use.

The value of growth monitoring

A multi-professional group met in Coventry in 1998 to discuss the benefits of growth monitoring in the UK [Hall 2000]. They concluded that routine monitoring in the pre-school years was neither sensitive nor specific enough to detect the slowly growing child with pathology and recommended that a single height measurement should be made at school entry. Since these guidelines have been published, many health authorities have abandoned routine height measurements in the pre-school years. While these conclusions may well be appropriate to detect children with chronic disorders, they are unlikely to identify those with future health risks.

Carter (2002) has pointed out *'a child with unmet health needs is on a trajectory to worsening health and well-being as an adult'*. Normal growth is a sign of good health but poor growth does not necessarily signify organic disease. At the very least, it may also be a marker for socio-economic deprivation [Voss et al 1998]. Ignoring the slowly growing child without pathology may well impose future suffering and increase health service costs. Mulligan et al (1998) have shown that height data collected by **trained** community personnel are comparable to those made in a research setting. Routine height measurements therefore

are of value in monitoring childhood growth but weight should also be incorporated. Both these variables contribute equally in the study of normal growth and development but the information gleaned is further increased by a comparison of the two.

The planning, training and cost involved in a national programme, however, should not be underestimated. Growth monitoring of all children is clearly a multidisciplinary exercise involving the cooperation and commitment of health visitors, school nurses, growth specialists and administrative personnel. Nevertheless, monitoring the growth of children from birth to adulthood while documenting health outcome, may ultimately improve the health of all and reduce the burden to society. Such a programme is inevitably long-term, requires central control and careful planning and implementation.

Further research

Although short adult stature is linked to poorer psychological function and increased health risks, the evidence is not conclusive. Most studies investigating psychosocial adaptation suffer from flaws in methodology [Voss 2001]. Wygold (2002) has highlighted the need for a growth-related questionnaire that evaluates subjective and objective perception of short stature. Similarly, there is a need to quantify the health risks facing short adults and to consider confounding variables such as low birth weight, poor social conditions and adult lifestyles, which themselves confer independent health risks and tend to co-exist [Silventoinen et al 1999, Barker et al 2001].

Even if the health risks of short adult stature can be quantified, it is uncertain whether the pharmacological manipulation of height will lead to improved well-being or is even possible for the short normal child. To date, the Wessex Growth Study is the only randomized control study of short normal children that has investigated the effect of growth hormone treatment on the pattern of growth and psychological well-being. While the effect on height outcome has been encouraging for treated girls [McCaughey et al 1998], this has not been replicated for the boys [unpublished data]. It should also be noted that although treatment resulted in at least a transient increase in growth velocity, it did not appear to confer any psychological advantage or disadvantage [Downie et al 1996]. There is a need for further studies to confirm these findings.

This study has shown that continued height monitoring after school entry is unlikely to detect new cases of pathology or identify those children who will become short adults. However, at the age of 5 years, the short normal children recruited to this study were already short for genetic expectations. Many were living in poor social conditions and were light at birth. As a rule, research studies investigating growth invariably concentrate on weight in early childhood and height in the school years. It is possible monitoring weight **and** height before school entry would be more effective in identifying those likely to become short adults and to suffer ill-health.

Synopsis

The Wessex Growth Study is the first study to monitor the patterns of growth of an unselected population of short normal children from the age of 5 years until final height. With the advantage of a control group of age- and gender-matched children of 'average' height, it has been able to observe and quantify the secular increase in height since the construction of the latest standards. Consequently, contrary to previous research, this study has demonstrated that many short normal children remain short with respect to their peers and genetic expectations. This is particularly so for girls and this study has also revealed previously undocumented gender differences in the patterns of growth of short normal children: although short normal boys and girls had similar genetic, environmental and health profiles at recruitment, only boys were likely to experience pubertal delay. This may have relevance for the clinical management of short normal children as those with later puberty tended to become the taller adults. Moreover, for both short and control groups, most girls experienced puberty within the expected age range but a clinical delay in the pubertal spurt was observed for 1 in 10 boys. This delay was preceded by a transient fall in height centile making them more likely to be referred for specialist opinion and which may explain why previous research has concluded that most short normal children attain a satisfactory height. Few other variables, genetic or environmental, were found to be predictors either of the pattern of growth or final height.

When faced with a short normal child, the clinician is indeed facing a dilemma. Short adults evidently have greater health risks and are psychosocially disadvantaged. This study has demonstrated the individuality of the growth pathway and the difficulty in identifying those who will become short adults. Nevertheless, it is the paediatrician's duty to respond to the needs of each child. This, however, is not the responsibility solely of the growth specialist.

Many factors, genetic, social and environmental, evolve together influencing both adult stature and health outcome. Recognising which children would benefit from intervention, whether pharmacological, psychological, or social, may ultimately improve their quality of life but requires the involvement of a multi-professional health team.

Chapter 7: MATHEMATICAL MODELLING: A VALIDATION STUDY

Mathematical models of growth are useful to summarize both the pattern and timing of growth in individuals and in populations. The Preece-Baines model has been used extensively in the study of longitudinal growth to describe the pattern of both normal and abnormal growth. This chapter compares the 'biological' parameters derived from this model with those presented in this thesis using methods devised specifically for the Wessex Growth Study.

7.1 Introduction

In 1978, Preece and Baines introduced a family of mathematical functions that describe the curve of growth from the age of two years to maturity. Three related models were developed, all of which simulate the shape of the individual growth curve. Since then, these models have been widely used to fit smoothed growth curves to longitudinal height data and generate biological parameters that characterise both the pattern and timing of growth. Model 1 in particular has been found to be robust, converging rapidly in most cases and has been extensively used in the study of longitudinal growth [Bogin et al 1992, Komlos et al 1992, Hauspie et al 1994, Koziel 1998, Beunen et al 2000, Koziel 2001]. This model has also proved useful for those with severely impaired growth [Milani 2000].

In the present study, biological parameters, such as age and magnitude of peak height velocity (PHV) and age at pubertal take-off, were estimated before the completion of growth from simple mathematical procedures utilising the height velocity curve. The aim of this chapter is to assess the validity of these procedures by comparing the estimates of the biological parameters obtained with those derived from the Preece-Baines model 1.

7.2 Subjects and Methods

The Preece-Baines Model 1 (P-B1) [Preece and Baines 1978], which takes the form:

$$h = h_1 - \frac{2(h_1 - h_0)}{\exp[s_0(t - theta)] + \exp[s_1(t - theta)]}$$

where h is height at time t, was fitted to the growth data of all short (56 boys, 47 girls) and control (62 boys, 52 girls) children who were followed from school entry (mean age 5.8

years) until final height. The number of measurements for each child ranged from 11 to 29 although most had at least 20 measurements (median 24). The fitting of the equation to the data was done by non-linear least squares and resulted in estimates of the five function parameters h_1, h_0, s_1, sh_0 and *theta* where:

> h_1 is final height, s_0 and s_1 are rate constants, *theta* is a time constant and h_0 is height at *theta*.

As described by Preece and Baines (1978), these parameters were used to derive estimates of age at take-off, velocity at take-off, height at take-off, age at PHV, magnitude of PHV, and height at PHV. The adolescent height gain was also calculated by subtracting height at take-off from adult height. The statistical package SPSS 10.0.5 was used to explore the data distribution of these biological parameters and to compare the growth patterns of both short and control groups.

Although mathematical modelling techniques are used generally to summarise and compare the patterns of growth in individuals, they can also be used to improve cross-sectional growth standards and to obtain population data [Hauspie 1988]. Strictly speaking, the control children were not a random population sample but were selected from a truncated population sample, described in Chapter 3, on the basis of their height at aged 5-7 years. Nevertheless, as adults, the heights of both males and females covered most of the normal range (-1.7sds to 2.1sds). Indeed, when these data were investigated the underlying distribution of adult height for both genders were found to be Gaussian as illustrated in figure 7.1 by the quantile-quantile (Q-Q) normality plots. The Kolmogorov-Smirnov's test of normality (K-S) also indicated normally distributed data for both girls (*K-S=0.098, p>0.200*) and boys (*K-S=0.070, p>0.200*). It is reasonable, therefore, to assume that the biological variables estimated from the P-B1 model are representative of the population. Therefore, to determine any secular trend in pubertal maturation one sample t-tests were performed comparing the mean age at PHV of control girls and boys with that of Tanner's original standards [Tanner et al 1966b] compiled over 30 years previously.

To assess the validity of the techniques used in this study (WGS method), the estimates obtained for the biological parameters characterising the pattern of growth were compared with those derived from the P-B1 model. These consisted of age and height at pubertal

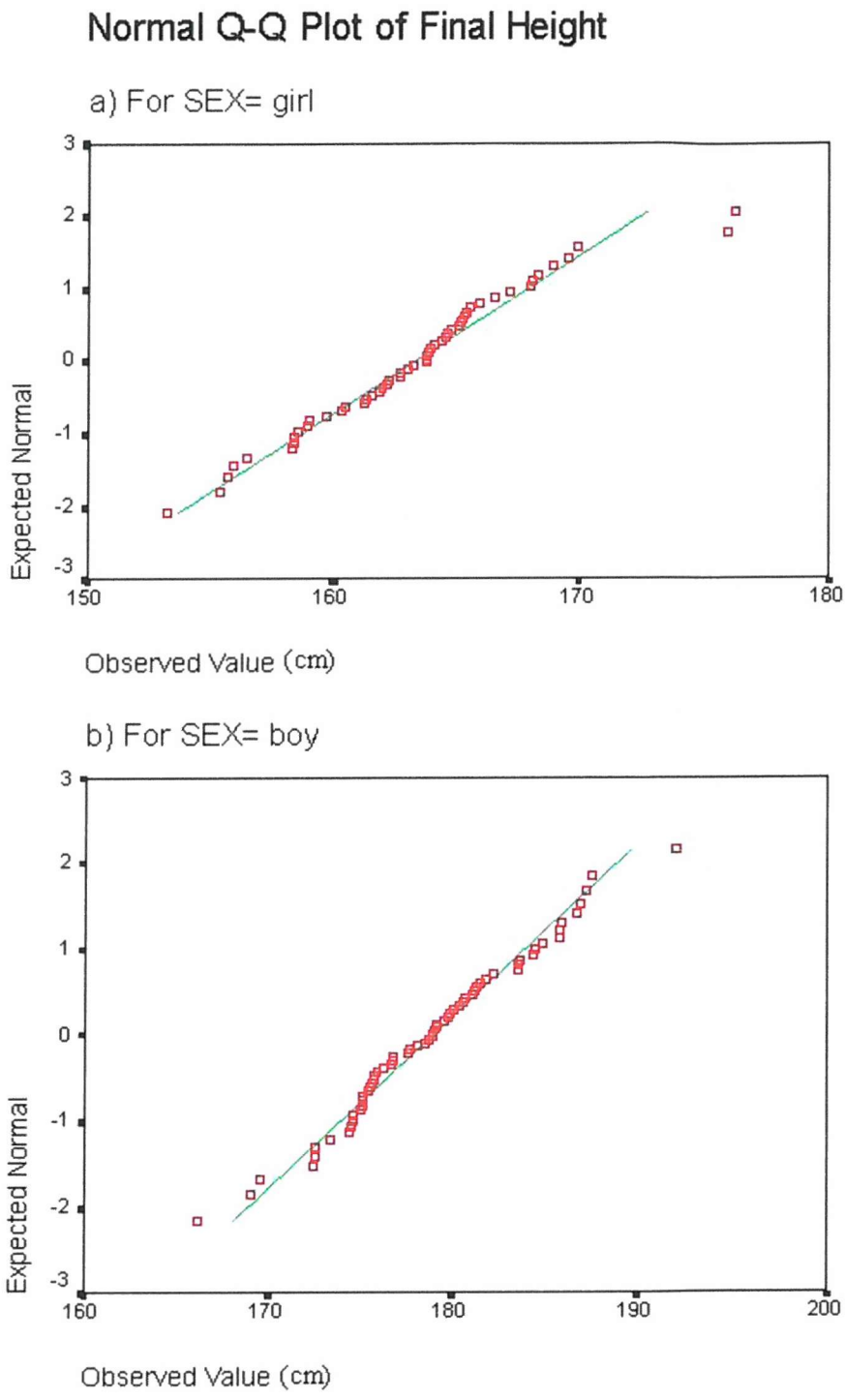


Figure 7.1 *Estimated final heights derived from Preece-Baines model 1 plotted against expected z scores for a) 52 control girls and b) 62 control boys*

take-off, the magnitude of PHV, the age and height at PHV, and final height. Means were compared using Student's t-test and where appropriate, analysis of covariance was used to determine the effect of height group and gender. Pearson's correlation coefficient was used to evaluate the associations between variables.

7.3 Results

All figures are shown at the end of this chapter.

The Preece-Baines model fit

The Preece-Baines model is considered to be robust and indeed, converged rapidly in all cases. The residual standard error, a measure of the overall fit, ranged between 0.254 and 1.104.

The model fitted best for those individuals whose growth patterns were well-behaved and where the flattening off of the growth process was easily discernible. An example of such a case is illustrated in figure 7.2. Poorer fits appeared to result from three factors, illustrated in figures 7.3 to 7.5. First, the Preece-Baines function is sensitive to missing data, especially at or after PHV [Milani 2000]. Inevitably, in a longitudinal study such as this, some missing measurements did occur resulting in a less accurate fit (figure 7.3). Second, in a few subjects the poor fit was the result of a single, apparently erroneous, measurement. This was particularly noticeable around the time of final height as in some instances height was measured immediately after rising from bed. In adults, the change in height due to diurnal variation may be as much as 2 cm [Krag et al 1990]. An example of such a case is shown in figure 7.4. Finally, an unusual or erratic pattern of grown, such as that illustrated in figure 7.5, also resulted in a poorer fit.

Preece-Baines biological parameters

The mean (SD) values for short and control groups of the seven biological variables estimated from the P-B1 model and the adolescent height gain are shown in table 7:1.

As expected, the control children were significantly taller than those who were short at the age of pubertal take-off, age at PHV and final height. For the girls in the study, the pubertal characteristics, that is the age and velocity at take-off, the age and magnitude of the pubertal

spurt and the adolescent height gain, were similar for both groups. However, for the boys, the pubertal spurt of the short group occurred significantly later and tended to be less intense, although in this case the difference did not quite reach significance level (table 7:1).

Table 7:1 *The biological parameters derived from the Preece-Baines Model 1 for short and control children followed to final height. Values shown are mean (SD)*

	SHORT	**CONTROL**	***p-value***
a) Girls	**N=47**	**N=52**	
Age at take-off (yr)	9.15 (0.95)	9.05 (1.07)	*0.604*
Velocity at take-off (cm/yr)	4.6 (0.5)	5.2 (0.7)	*<0.001*
Height at take-off(cm)	118.6 (4.7)	130.8 (4.7)	*<0.001*
Age at PHV (yr)	12.28 (0.94)	11.92 (0.98)	*0.071*
Magnitude of PHV (cm/yr)	7.7 (0.8)	7.6 (1.0)	*0.809*
Height at PHV (cm)	136.8 (4.0)	148.7 (4.2)	*<0.001*
Adult height (cm)	150.7 (4.2)	163.3 (4.6)	*<0.001*
Adolescent height gain (cm)	32.0 (4.0)	32.5 (5.3)	*0.631*
b) Boys	**N=56**	**N=62**	
Age at take-off (yr)	10.90 (0.91)	10.46 (1.15)	*0.025*
Velocity at take-off (cm/yr)	4.3 (0.5)	4.8 (0.5)	*<0.001*
Height at take-off(cm)	127.7 (4.8)	140.9 (6.6)	*<0.001*
Age at PHV (yr)	14.48 (0.94)	13.82 (1.12)	*0.001*
Magnitude of PHV (cm/yr)	8.9 (1.3)	9.4 (1.3)	*0.052*
Height at PHV (cm)	149.1 (4.1)	162.9 (5.2)	*<0.001*
Adult height (cm)	164.5 (4.4)	178.9 (5.0)	*<0.001*
Adolescent height gain (cm)	36.9 (4.0)	38.0 (4.8)	*0.319*

The data distributions of the five variables that characterise the pubertal spurt, that is age and velocity at take-off, age and magnitude of PHV and the adolescent height gain, were examined using the Kolmogorov-Smirnov test to assess normality (table 7:2). All parameters were found to be normally distributed except for age at PHV for short and control boys and for the pubertal height gain of control boys. Figure 7.6 show the Q-Q normality plots and

figure 7.7 the boxplot representations of the age at PHV for short and control boys. These indicate a positively skewed distribution for both groups. For the short boys, coefficients of skewness and kurtosis were, respectively, 0.496, *p=0.119* and -0.312, *p=0.617* while the corresponding values for the control boys were 0.671, *p=0.027* and -0.094, *p=0.873*. The Q-Q normality plot and boxplot representation of the adolescent gain in height for the control boys are shown in figure 7.8. In this case, the skewness and kurtosis coefficients were both non-significant but 5 control boys, whose adolescent height gain was estimated to be greater than 47cm, were identified as outliers.

Table 7:2 *The data distributions of the five pubertal parameters estimated by the Preece-Baines model were examined. Results show the Kolmogorov-Smirnov (K-S) statistic for Short and Control girls and boys.*

	SHORT		**CONTROL**	
	K-S statistic	***p-value***	**K-S statistic**	***p-value***
a) Girls	**N=47**		**N=52**	
Age at take-off (yr)	0.072	*>0.200*	0.094	*>0.200*
Velocity at take-off (cm/yr)	0.088	*>0.200*	0.067	*>0.200*
Age at PHV (yr)	0.066	*>0.200*	0.081	*>0.200*
Magnitude of PHV (cm/yr)	0.099	*>0.200*	0.097	*>0.200*
Adolescent height gain (cm)	0.103	*>0.200*	0.091	*>0.200*
b) Boys	**N=56**		**N=62**	
Age at take-off (yr)	0.078	*>0.200*	0.102	*0.174*
Velocity at take-off (cm/yr)	0.086	*>0.200*	0.074	*>0.200*
Age at PHV (yr)	0.121	*0.040**	0.143	*0.003**
Magnitude of PHV (cm/yr)	0.102	*>0.200*	0.063	*>0.200*
Adolescent height gain (cm)	0.112	*0.075*	0.125	*0.018**

** denotes significant result*

In the control group, the expected gender differences were apparent for both the intensity and timing of the adolescent spurt: control boys had a more intense spurt that occurred approximately 2 years later than that of control girls. The mean gender difference (95% confidence limits) in the magnitude of PHV was 1.74 (1.32 to 2.17) cm/yr, and in the age at PHV was 1.90 (1.50 to 2.29) years. One sample t-tests did not reveal any significant differences in the mean age at PHV either for control girls (*p=0.577)* or for control boys

($p=0.217$) compared with the standards of Tanner et al (1966b) but the magnitude of the peak was somewhat less for control girls ($p<0.001$) though not for control boys ($p=0.614$).

The correlation coefficients between adult height and the pubertal parameters derived from the P-B1 model are shown in table 7:3 and table 7:4 for short and control groups, respectively.

Table 7:3 *Correlation matrix for pubertal parameters estimated from the Preece-Baines model for a) 52 Control girls and b) 62 Control boys. Results show correlation coefficients and p-values*

	Take-off			Peak Height Velocity		
	Age	**Velocity**	**Height**	**Age**	**Velocity**	**Height**
a) Control Girls						
Take-off velocity	-0.56 *(<0.001)*	-				
Take-off height	0.82 *(<0.001)*	-0.14 *(0.321)*	-			
Age at PHV	0.93 *(<0.001)*	-0.69 *(<0.001)*	0.64 *(<0.001)*	-		
Magnitude PHV	-0.51 *(<0.001)*	0.31 *(0.026)*	-0.45 *(0.001)*	-0.40 *(0.003)*	-	
Height at PHV	0.57 (<0.001)	0.04 *(0.763)*	0.84 *(<0.001)*	0.54 *(<0.001)*	-0.06 *(0.684)*	-
Adult height	0.14 *(0.317)*	0.39 *(0.004)*	0.50 *(<0.001)*	0.19 *(0.185)*	0.15 *(0.276)*	0.86 *(<0.001)*
b) Control Boys						
Take-off velocity	-0.66 *(<0.001)*	-				
Take-off height	0.76 *(<0.001)*	-0.21 *(0.097)*	-			
Age at PHV	0.96 *(<0.001)*	-0.75 *(<0.001)*	0.64 *(<0.001)*	-		
Magnitude PHV	-0.62 *(<0.001)*	0.43 *(<0.001)*	-0.38 *(0.003)*	-0.66 *(<0.001)*	-	
Height at PHV	0.52 *(<0.001)*	0.01 *(0.928)*	0.91 *(<0.001)*	0.45 *(<0.001)*	-0.13 *(0.330)*	-
Adult height	0.21 *(0.098)*	0.25 *(0.048)*	0.68 *(<0.001)*	0.19 *(0.133)*	0.08 *(0.534)*	0.92 *(<0.001)*

Table 7:4 *Correlation matrix for pubertal parameters estimated from the Preece-Baines model for a) 47 Short girls and b) 56 Short boys. Results show correlation coefficient and p-value*

	Take-off			Peak Height Velocity		
	Age	**Velocity**	**Height**	**Age**	**Velocity**	**Height**
a) Short Girls						
Take-off velocity	-0.76 *(<0.001)*	-				
Take-off height	0.89 *(<0.001)*	-0.46 *(0.001)*	-			
Age at PHV	0.95 *(<0.001)*	-0.79 *(<0.001)*	0.81 *(<0.001)*	-		
Magnitude PHV	-0.25 *(0.092)*	0.11 *(0.456)*	-0.19 *(0.195)*	-0.23 *(0.128)*	-	
Height at PHV	0.70 *(<0.001)*	-0.26 *(0.080)*	*0.87* *(<0.001)*	0.73 *(<0.001)*	0.05 *(0.721)*	-
Adult height	0.35 *(0.017)*	0.09 *(0.544)*	0.59 *(<0.001)*	0.46 *(0.001)*	0.12 *(0.424)*	0.90 *(<0.001)*
b) Short Boys						
Take-off velocity	-0.70 *(<0.001)*	-				
Take-off height	0.71 *(<0.001)*	-0.13 *(0.334)*	-			
Age at PHV	0.93 *(<0.001)*	-0.73 *(<0.001)*	0.54 *(<0.001)*	-		
Magnitude PHV	0.00 *(0.977)*	-0.05 *(0.729)*	-0.12 *(0.396)*	-0.10 *(0.458)*	-	
Height at PHV	0.55 *(<0.001)*	0.07 *(0.621)*	0.87 *(<0.001)*	0.52 *(<0.001)*	0.06 *(0.662)*	-
Adult height	0.29 *(0.033)*	0.27 *(0.043)*	0.60 *(<0.001)*	0.35 *(0.008)*	0.12 *(0.390)*	0.92 *(<0.001)*

These results confirm the predictability of height. The correlation between adult height and height at the start of the spurt was of the order of 0.5 to 0.7 and, regardless of height group or gender, increased to approximately 0.9 at peak height velocity. The whole pubertal process

was also highly correlated and to a large extent, was similar for both groups. For example, age at PHV correlated positively with height at take-off but negatively with height velocity at this time. In both groups, those with a later spurt tended to be taller at the start of the spurt but to be growing at a slower rate. Some group differences, however, were also apparent. For the control group, the magnitude of PHV tended to be higher for those boys and girls with earlier puberty although adult height was not influenced either by the timing or by the magnitude of the spurt. By contrast, there was no significant association between the age and magnitude of PHV for short boys or for short girls but those short children with a later spurt tended to become the taller adults.

Comparison with the present study

Where possible, estimates of the Preece-Baines biological parameters were compared with the corresponding estimates derived from the alternative, more direct methods used in the present study. Figure 7.9 illustrates the level of agreement between the methods for each variable and the results of paired t-tests are shown in table 7:5.

Table 7:5 *Results of paired t-tests comparing the estimates of biological parameters calculated in this study (WGS) with those derived from the Preece-Baines model (P-B1)*

	N	P-B1	WGS	Difference	*p-value*
Age at take-off (yrs)	211	9.98	10.67	-0.69	*<0.001*
Height at take-off (cm)	211	130.4	134.2	-3.8	*<0.001*
Age at PHV (yrs)	210	13.23	13.24	-0.01	*0.790*
Magnitude of PHV (cm/yr)	210	8.49	9.05	-0.56	*<0.001*
Height at PHV (cm)	210	150.5	150.4	0.1	*0.344*
Adult height (cm)	217	165.3	165.2	0.1	*0.016*

There was generally good agreement between the methods with correlation coefficients ranging between 0.85 and >0.99 (figure 7.9). Some systematic bias, however, was apparent and significant differences between the methods were found for age at pubertal take-off, height at pubertal take-off, the magnitude of PHV and final height (table 7:5). Analyses of covariance, however, did not reveal any significant group effects or, with the exception of the magnitude of PHV, gender effects. For this variable, the P-B1 method tended to have lower estimates than the WGS method but the degree of under-estimation was greater for boys than

for girls (*Girls: -0.41cm/yr, Boys: -0.68cm/yr, $p=0.001$*). However, as illustrated in figure 7.10, this appeared to be the result of differences in methodology rather than a true gender difference. As PHV increased, the under-estimation also increased (*$r=-0.409$, $p<0.001$*). Thus, as girls generally have a less intense peak than boys, a significant difference occurred.

Consistency between the two methods was best for the age at PHV. The mean difference was close to zero (table 7:5) and as shown in figure 7.11, the difference was less than 6 months for most individuals. Nevertheless, even for this variable, large discrepancies were evident for a few individuals. Mathematical models expect the presence of a clear adolescent growth spurt [Hauspie 1988]. Interestingly, for those individuals with large discrepancies, investigation of the height velocity curve revealed unusual patterns of adolescent growth. Some examples are shown in figures 7.12 to 7.15.

A small but significant difference in the mean final height was also found between the methods (table 7:5). According to the P-B1 method, the cohort was, on average, 0.1 cm taller suggesting that the participants had not quite reached final height. In the Wessex Growth Study, final height was taken as the last recorded measurement provided that this occurred at least three years after the occurrence of PHV. Figure 7.16 shows the difference between the methods for each participant. In some individuals, the difference was over 1 cm. Growth, however, is reported to continue as much as 10 years after PHV [Roche and Davila 1972, Hulanicka and Kotlarz 1983]. It might have been expected, therefore, that the discrepancy was related to the interval between age at PHV and age at final measurement but no significant correlation was found (*$r=.-0.08$, $p=0.264$*)

7.4 Discussion

To a large extent, the results from the P-B1 model agree with much of the findings reported in this thesis regarding differences in the patterns of growth of short normal and 'average' height children. As expected, the control children were significantly taller at pubertal take-off and the adolescent height gain was similar for short and control girls and for short and control boys (table 7:1) confirming that the height advantage of the taller control group was established in childhood, before the onset of the pubertal spurt.

These data also confirm the gender/group effects observed in this study concerning the pubertal growth of short and control children. In the control group, the pubertal spurt

occurred, on average, close to the population mean for both boys and girls. The characteristics of the pubertal spurt were similar for both short and control girls; no statistical differences were found between the groups in the age at take-off, age at PHV, magnitude of PHV or in the adolescent height gain (table 7:1a). By comparison, the pubertal spurt of short boys was later and less intense than that of the taller controls (table 7:1b). The data presented in this chapter also confirm that for short children, early maturation is ***not*** accompanied the usual higher compensatory peak [Tanner et al 1966b]. A significant negative correlation between the age at PHV and the magnitude of the pubertal spurt was found only for the control group (table 7:3 and table 7:4).

Nevertheless, although both the WGS and P-B1 methods depict similar patterns of growth for short and control boys and girls, significant differences were observed for several of the derived biological parameters, particularly with regard to the start of the adolescent spurt. Compared to the method used in this study, the P-B1 model estimated this to occur approximately 8 months earlier and consequently, the mean height of the cohort at this point was almost 4 cm shorter. The age at take-off, however, where prepubertal deceleration changes to into adolescent acceleration, is difficult to determine precisely. In a comparison of mathematical models of stature growth, Ledford and Cole (1998) observed that the Preece-Baines model tended to under-estimate the start of the pubertal spurt and concluded that the loss of accuracy resulted from the simpler form of velocity and acceleration derived from this model.

The adolescent peak is normally a distinct event and the characteristics of growth at the time of PHV are generally well modelled [Ledford and Cole 1998, Milani 2000]. Indeed, the P-B1 method yielded similar values to those derived in this study for the mean age at PHV and height attained at PHV but the magnitude of the peak was somewhat lower (table 7:5). It should be noted, however, that for both short and control children, the mean values of PHV calculated using the WGS method were found to be close to Tanner's mean values of 8.33cm/yr and 9.46cm/yr for boys and girls, respectively (see Chapter 4). Indeed, Preece and Baines (1978) themselves point out that the one parameter their models do not fit well is the magnitude of peak height velocity. It is also of interest to note the mean value of PHV estimated from the P-B1 model was significantly less that Tanner's mean value for control girls but similar for control boys.

The mean final height of the cohort was slightly but significantly higher using the P-B1 method. Late adolescent growth in stature has been observed [Roche and Davila 1972] and it may be that this small difference signifies growth to come. Height measurement, however, is not precise and at any instant, height can only be measured to within ±0.5cm [Voss et al 1991b]. Nevertheless, for many individuals the discrepancy in final height between the methods exceed 0.5 cm (figure 7.16). It should be remembered, however, that the body height of any individual is not fixed. Diurnal variation may substantially affect the reliability of height data [Voss and Bailey 1997]. During the course of a day, height loss of over 2 cm has been attributed to diurnal variation [Krag et al 1990] though the loss may be more rapid for those involved in weight-bearing employment [Tyrrell et al 1985]. In this study, the final height of some participants was measured immediately after rising while others were measured after a full day's manual employment. Indeed, large discrepancies could generally be ascribed to this source of error.

7.5 Summary

The biological parameters derived from the Preece-Baines model substantiate the findings of this study regarding the patterns of growth of short normal and control children. Methodological differences between the methods devised for this study and the Preece-Baines model resulted in significant differences in the mean values of some biological parameters. In particular, the Preece-Baines model appeared to underestimate the age at pubertal take-off and the magnitude of the pubertal spurt. Nevertheless, these differences were independent of height group or gender. Indeed, the data presented here demonstrate that the methods devised for the Wessex Growth Study depict a fair and reasonable summary, which characterise the pattern and timing of growth of individuals with very different heights and of a population of very short and average height children.

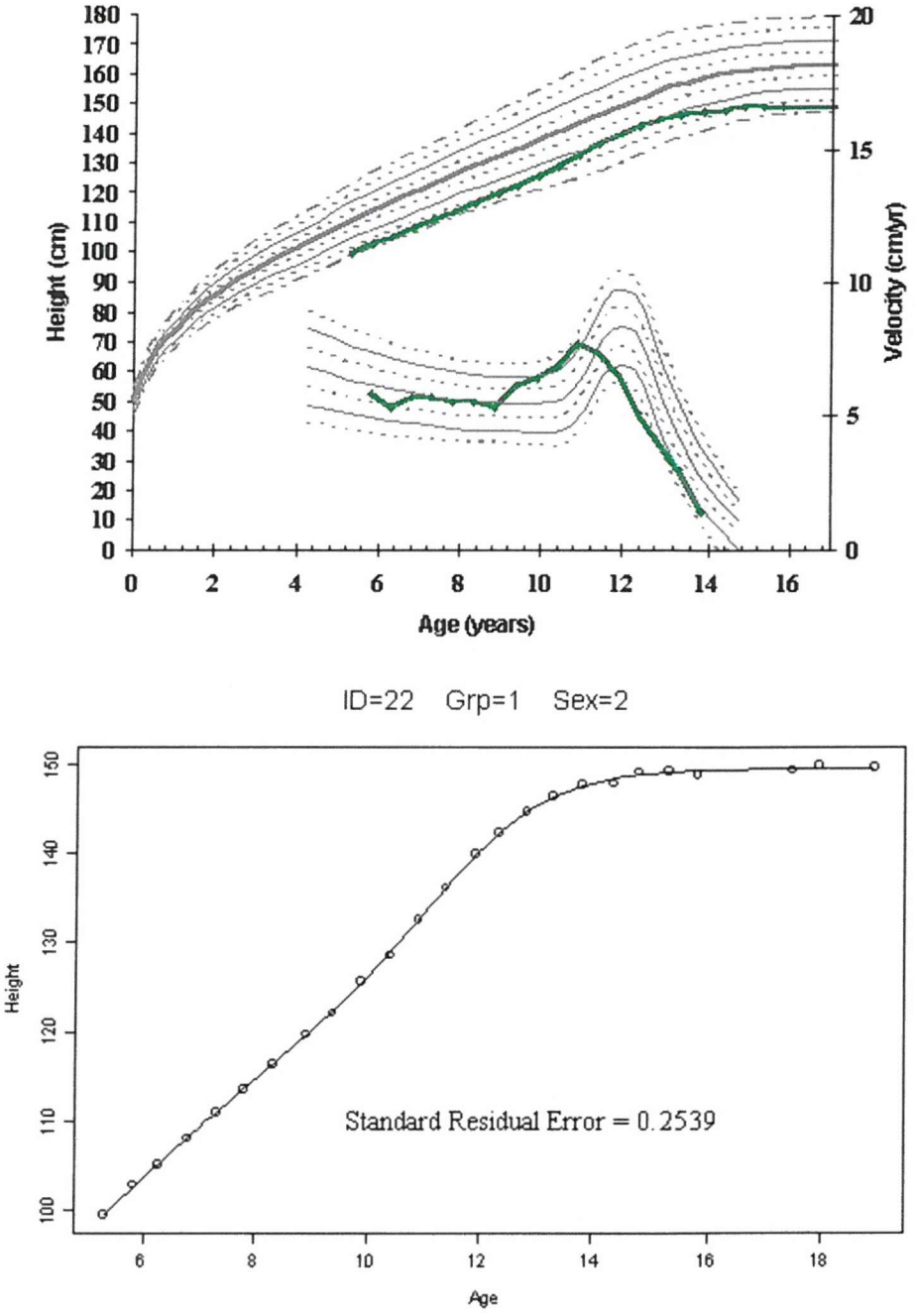


Figure 7.2 *When the pattern of growth was well-behaved and measurements continued until growth ceased (top), the Preece-Baines curve fitting routine simulated the shape of the growth curve with good precision (bottom)*

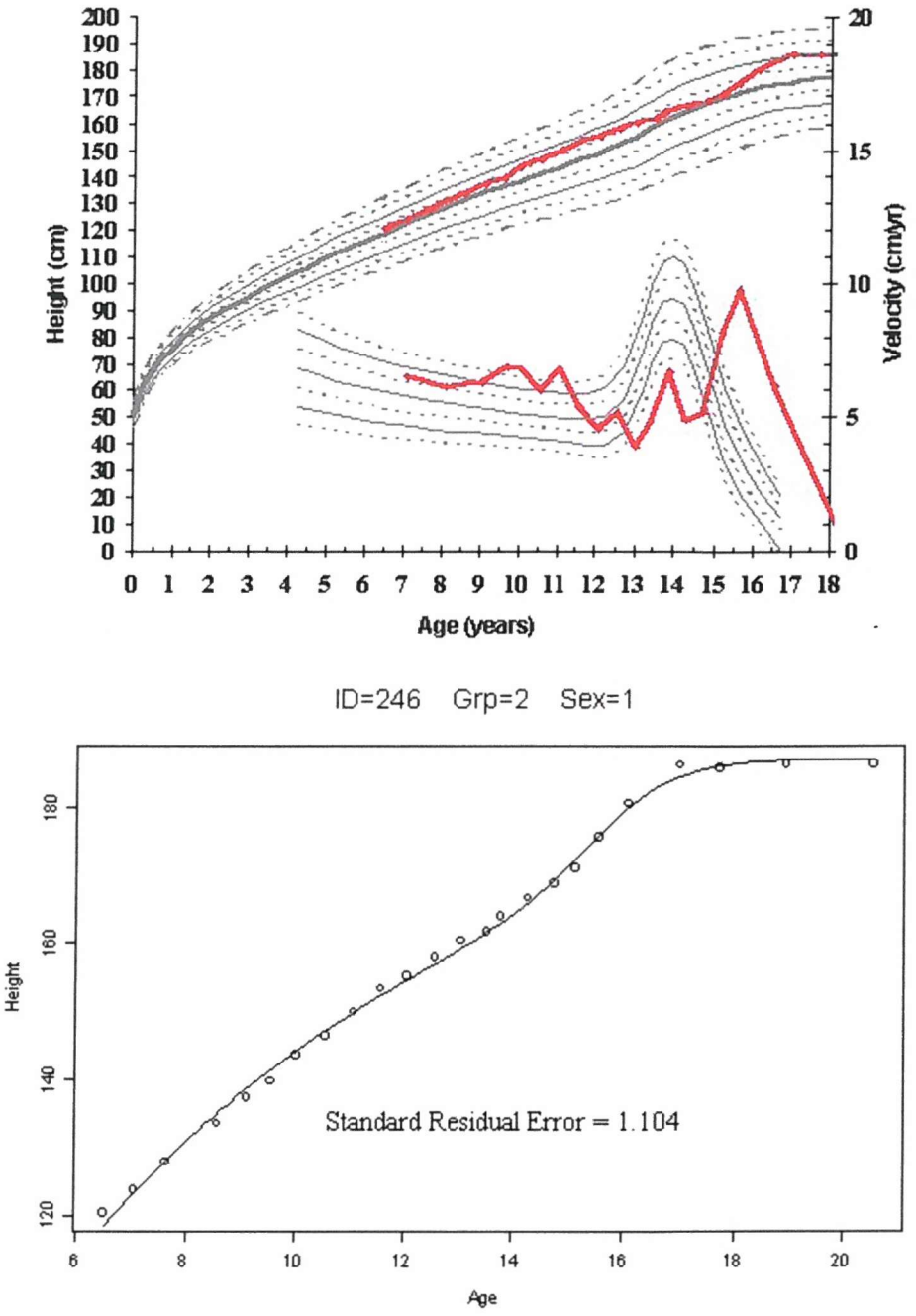


Figure 7.3 *Missing measurements around the time of PHV resulted in a less accurate fit from the Preece-Baines model*

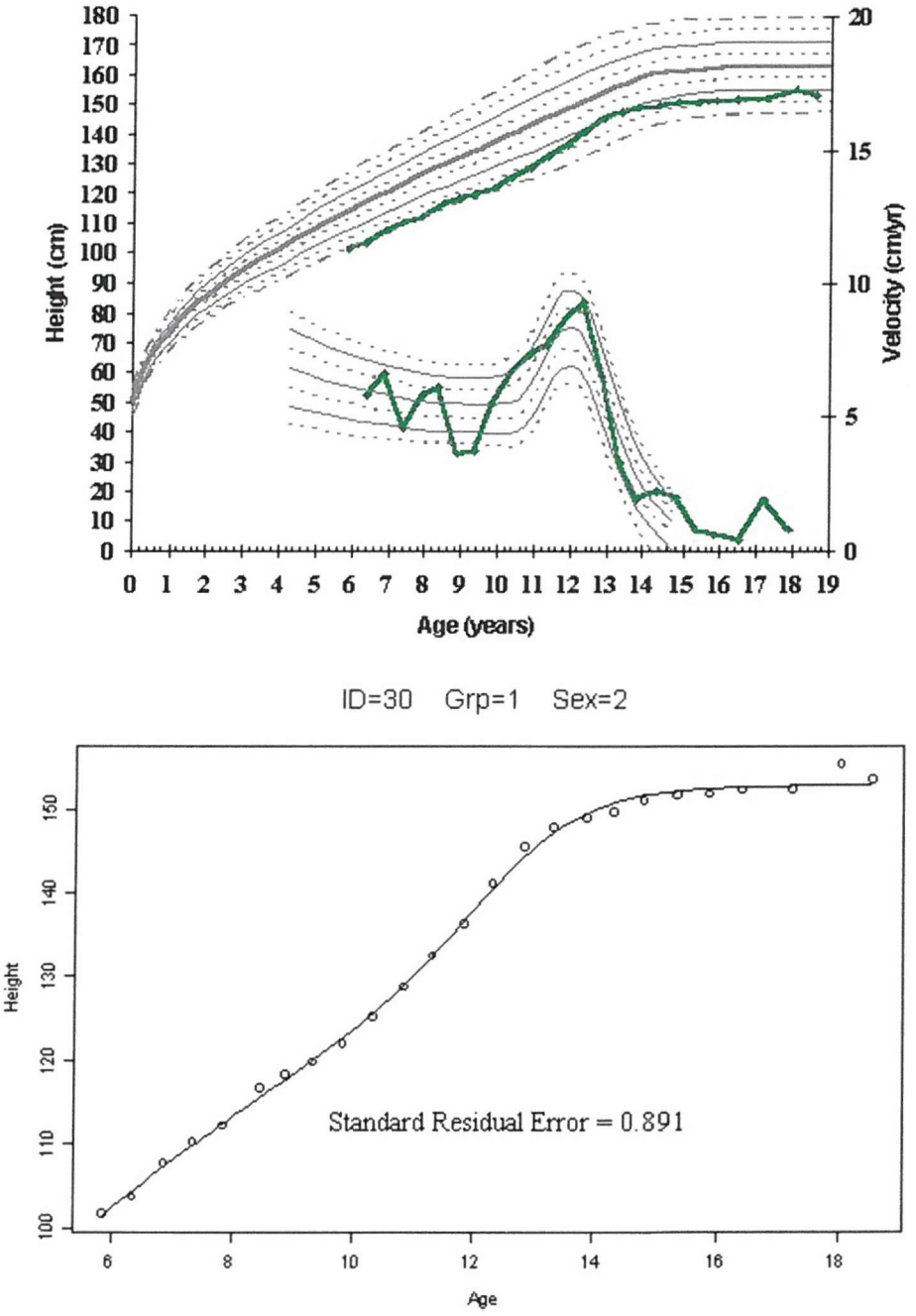


Figure 7.4 *A poorer fit from the Preece-Baines model could result from a single, apparently erroneous error*

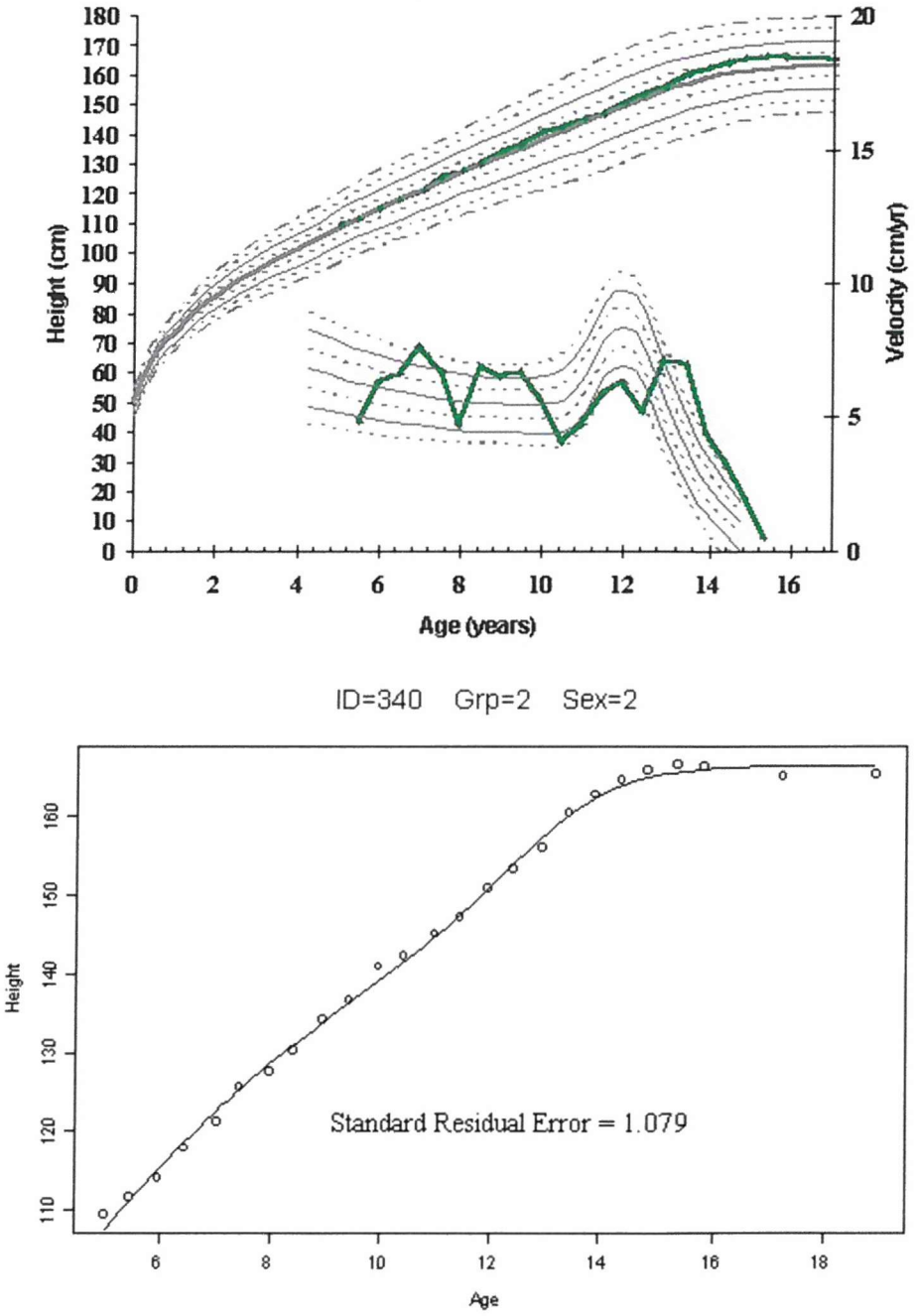


Figure 7.5 *This rather erratic pattern of growth (top) resulted in a relatively poor fit from the Preece-Baines model*

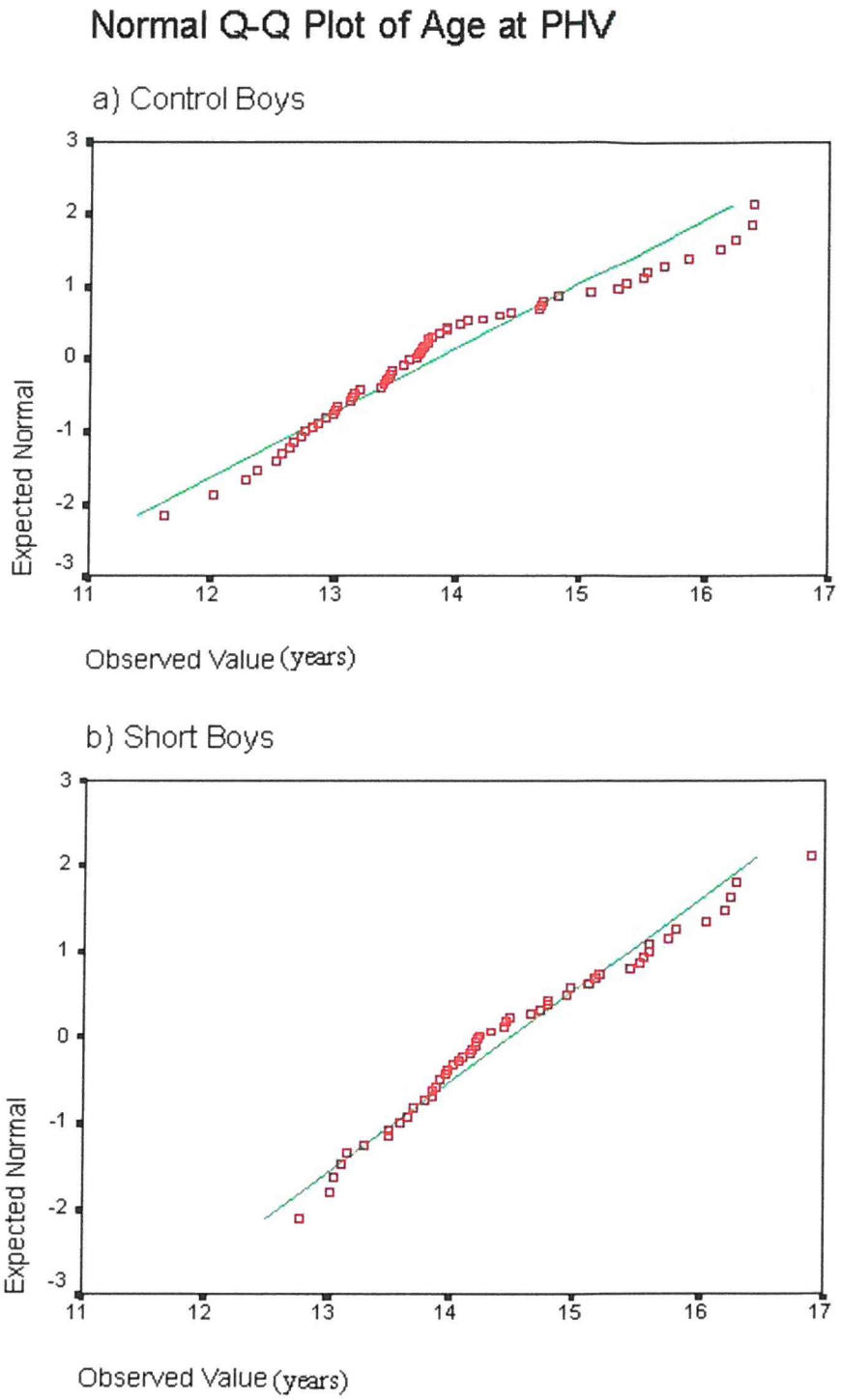


Figure 7.6 *Normality plot of the age at PHV for a) 62 control boys and b) 56 short boys*

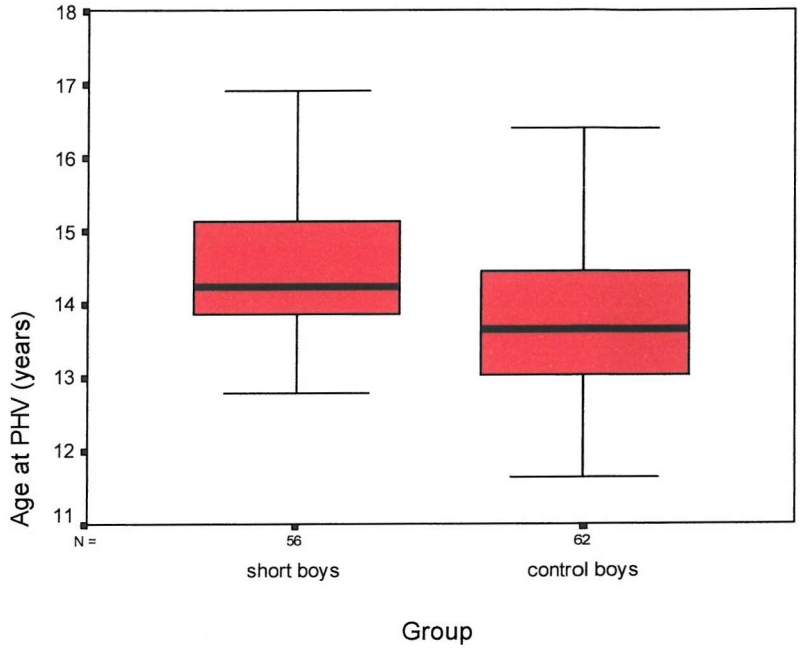


Figure 7.7 *Boxplot representation of the distribution of age at PHV of 56 short and 62 control boys*

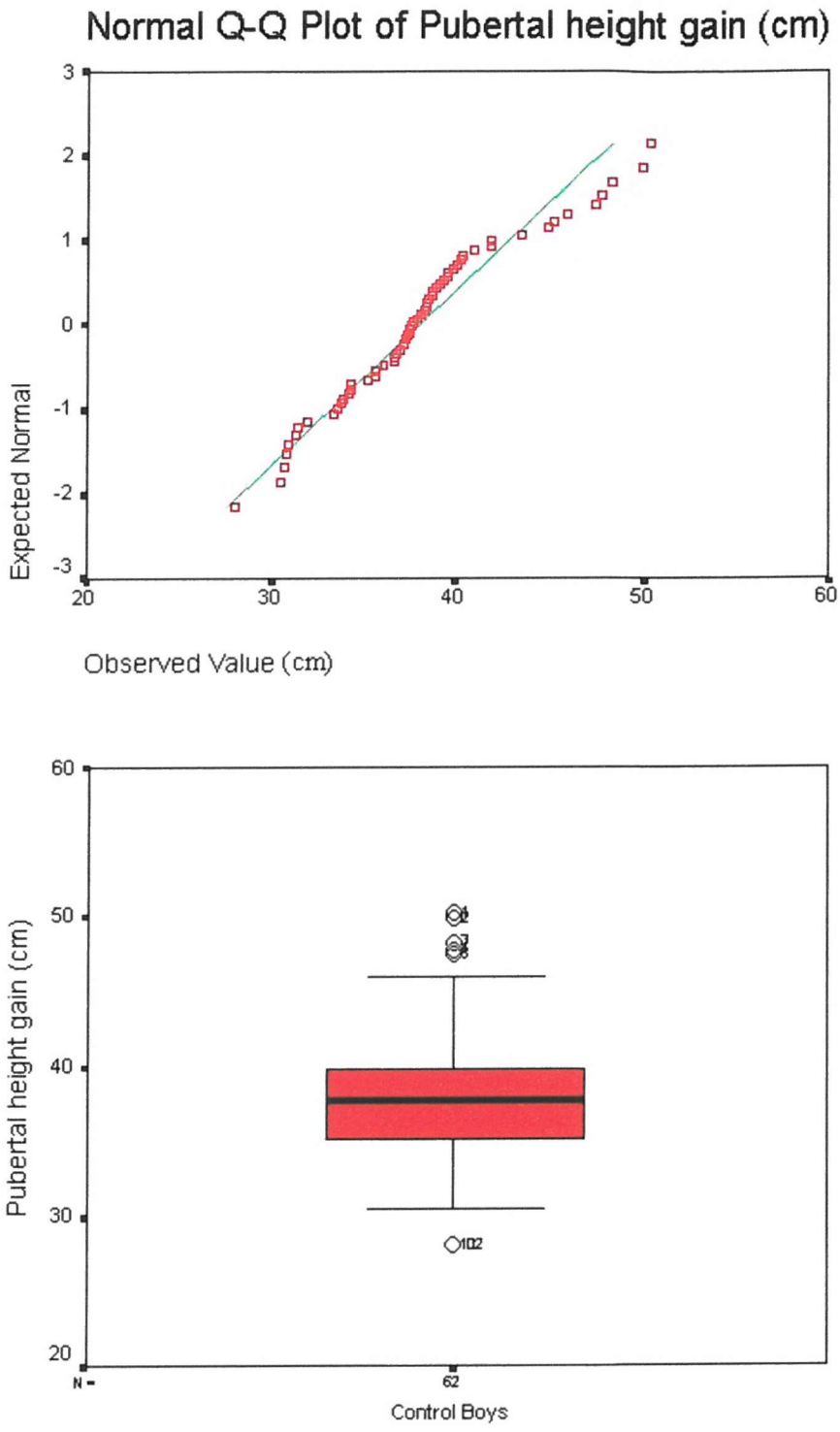


Figure 7.8 *Normality plot and boxplot representation of the pubertal height gain (cm) of 62 control boys*

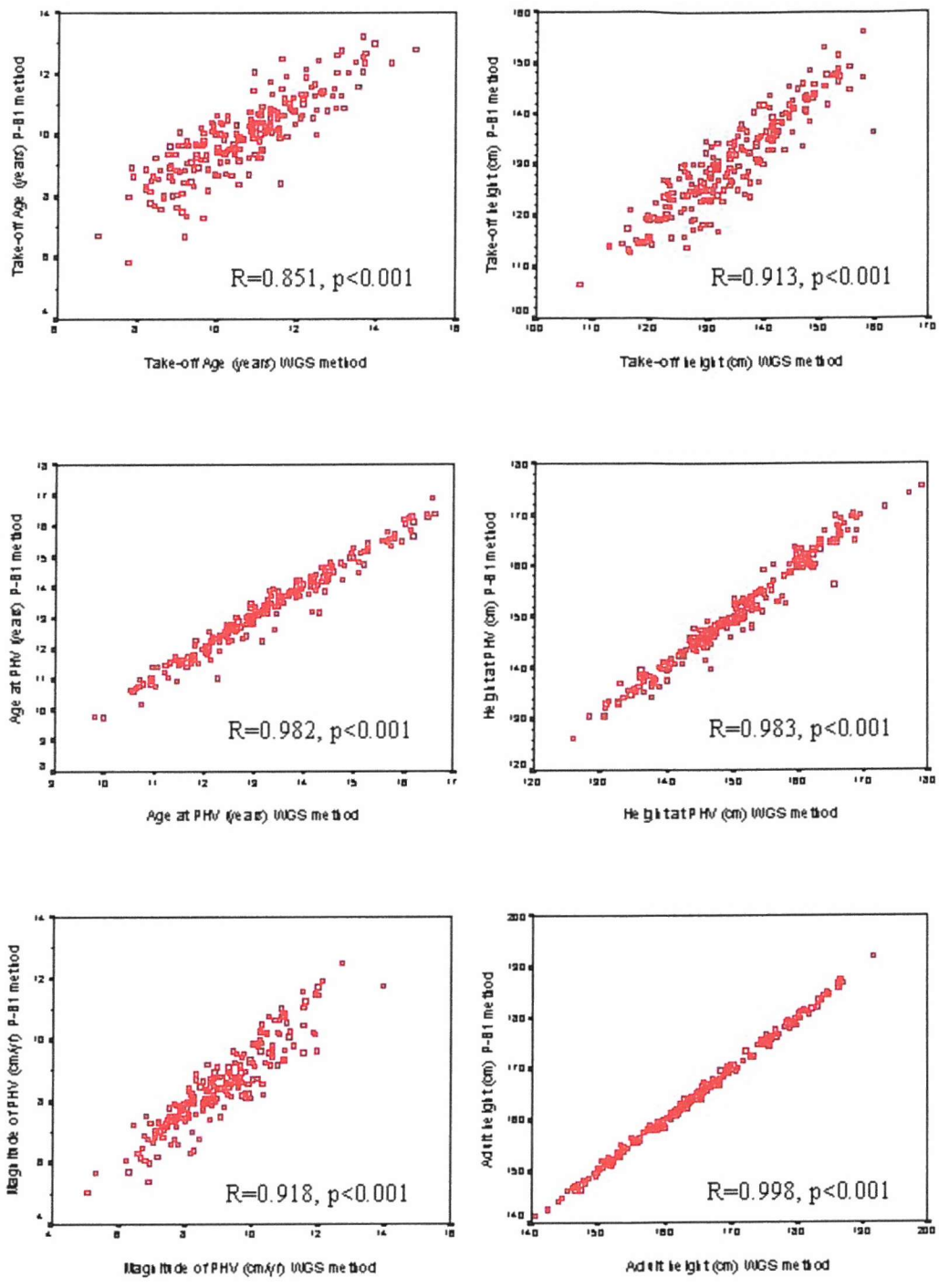


Figure 7.9 *Correlation of P-B1 and WGS methods for each biological parameter estimated*

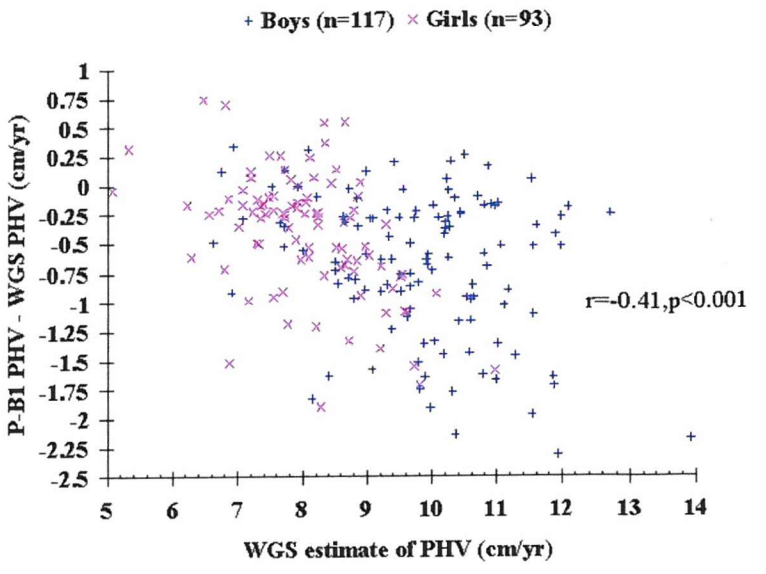


Figure 7.10 *Differences in estimates of PHV derived from the P-B1 method and from the WGS method were plotted against the WGS estimate*

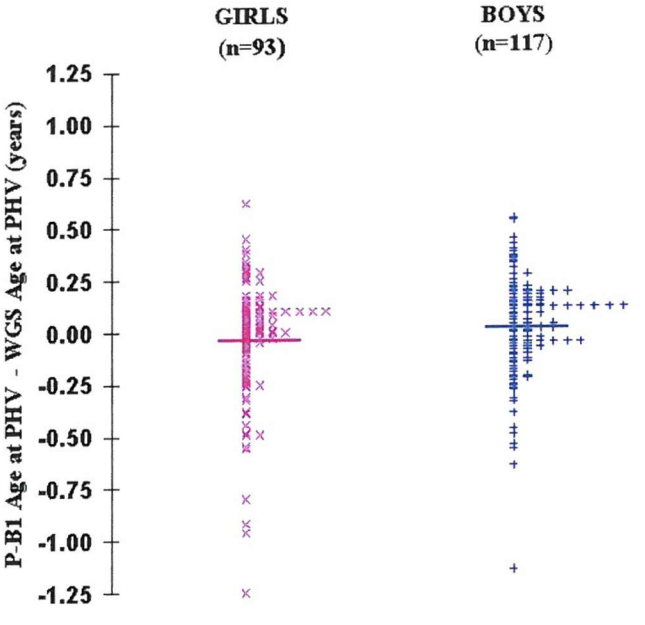


Figure 7.11 *The difference between estimates of the age at PHV derived from the P-B1 method and the WGS method for each individual. The mean difference was similar for boys and girls*

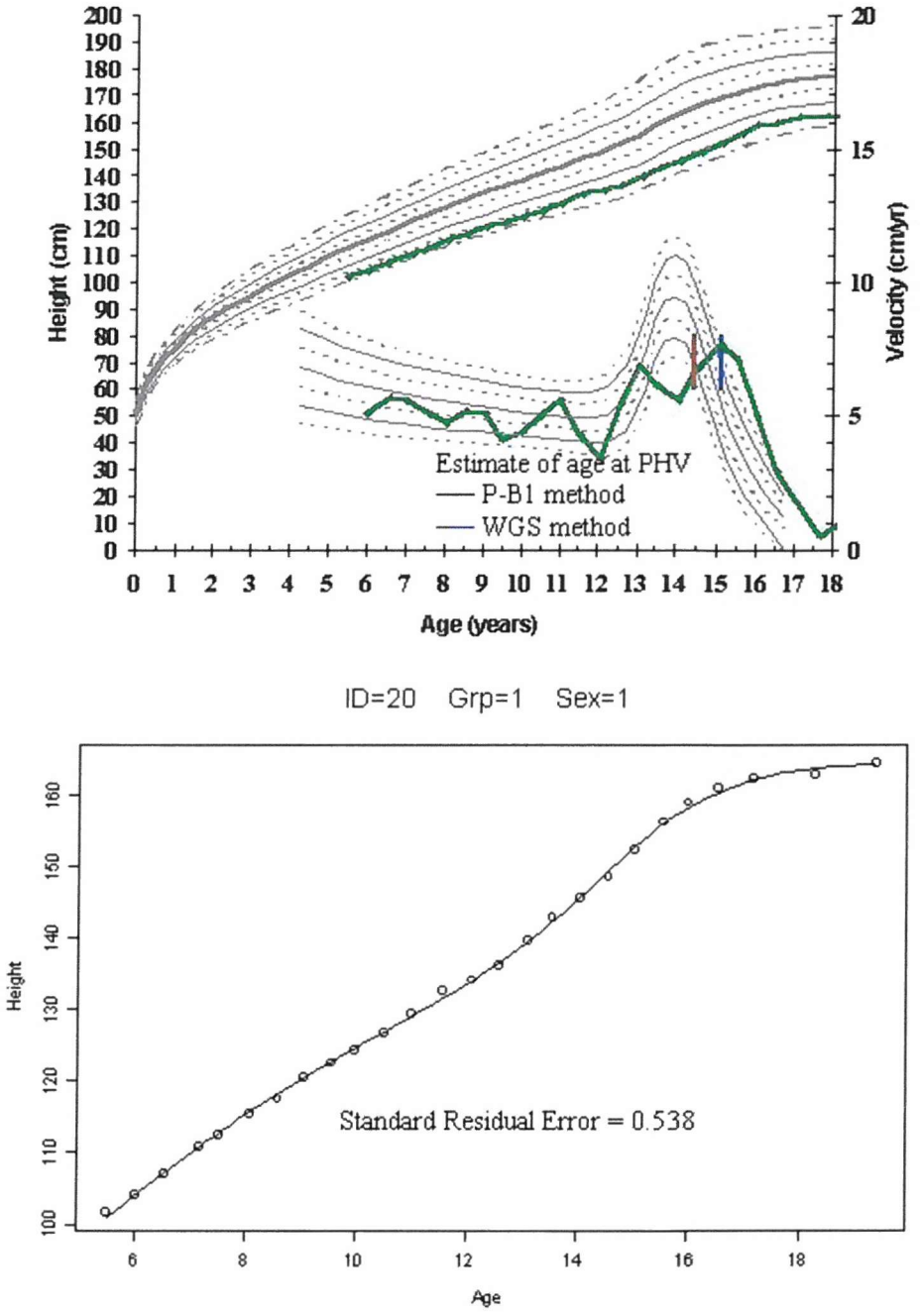


Figure 7.12 *A large discrepancy in the estimates of age at PHV occurred for this boy with an unusual pattern of adolescent growth*

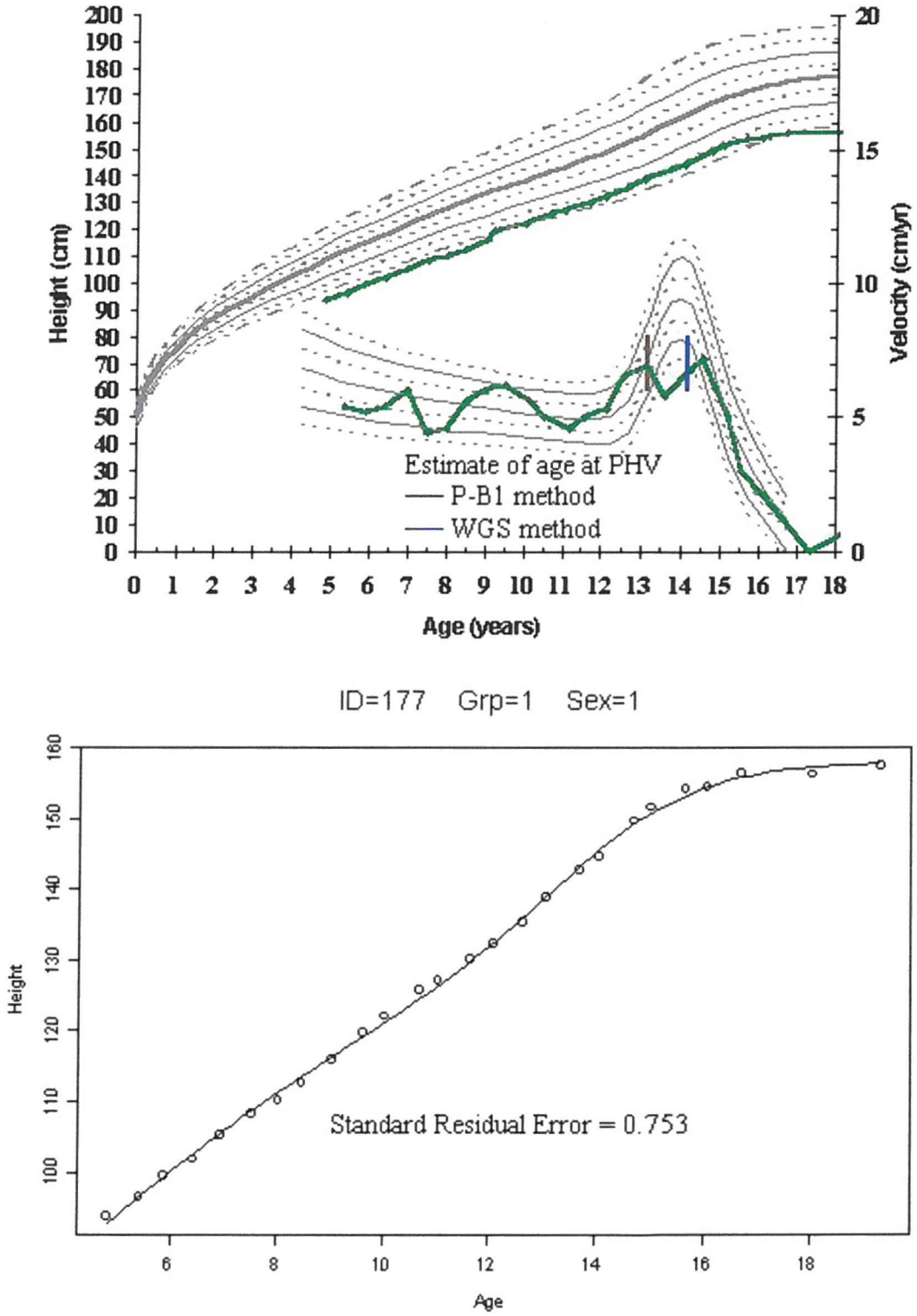


Figure 7.13 *The double peak of this boy's pubertal spurt caused a large discrepancy in the estimates of age at PHV*

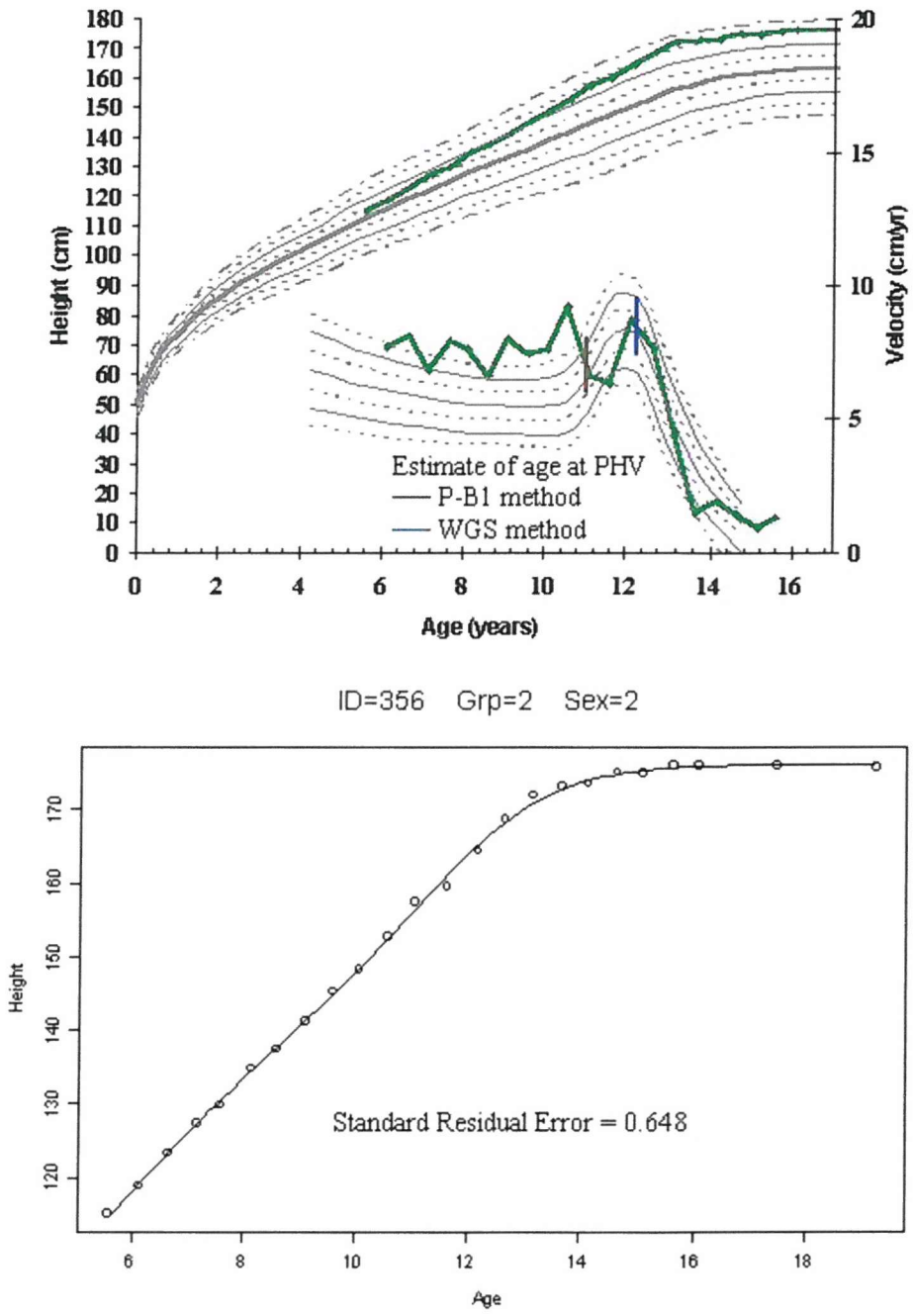


Figure 7.14 *This girl's pubertal spurt was smaller in magnitude than her pre-pubertal velocity causing age at PHV to be estimated incorrectly by the P-B1 method*

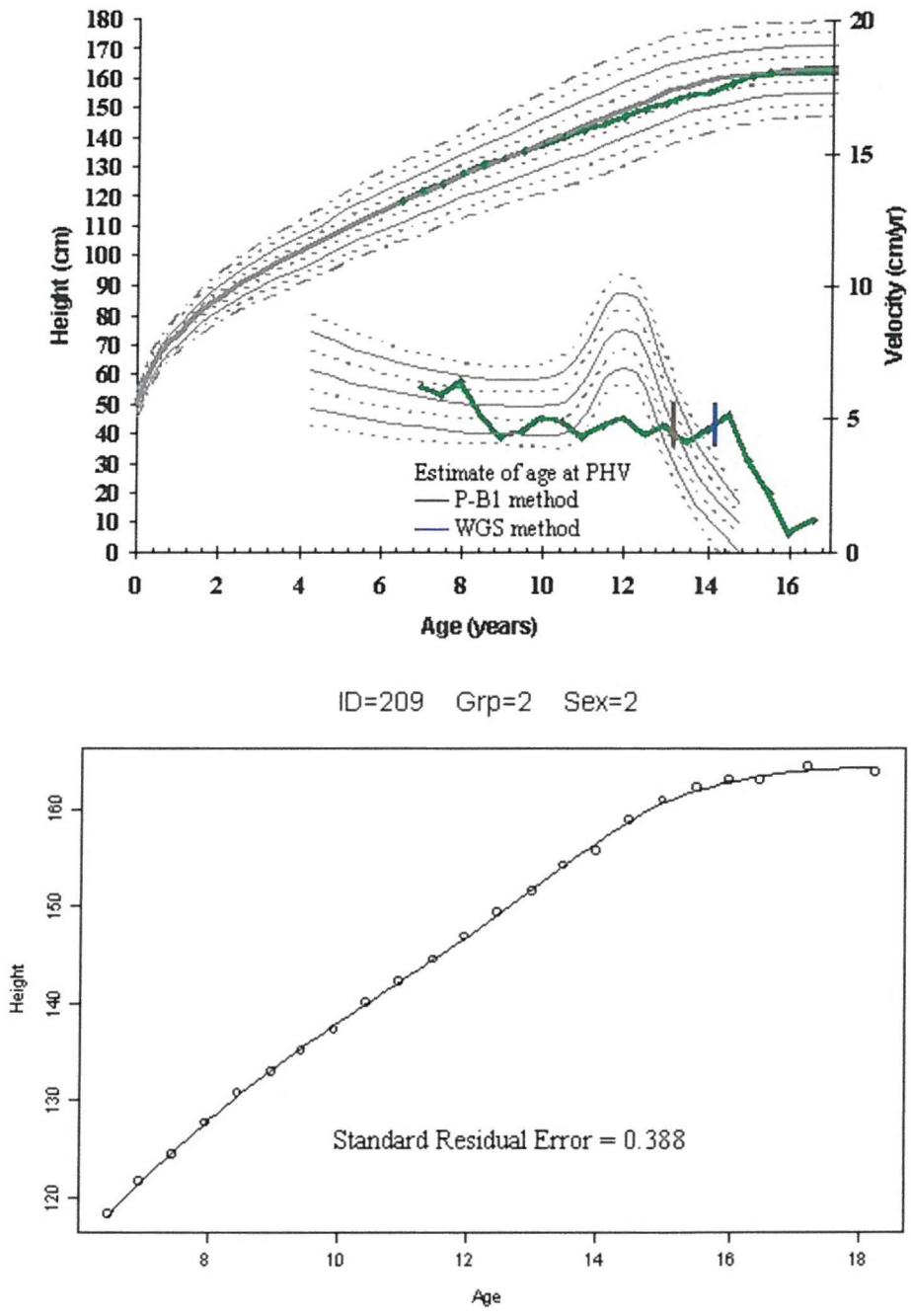


Figure 7.15 *This girl's pubertal peak was barely visible causing the P-B1 model to underestimate her age at PHV*

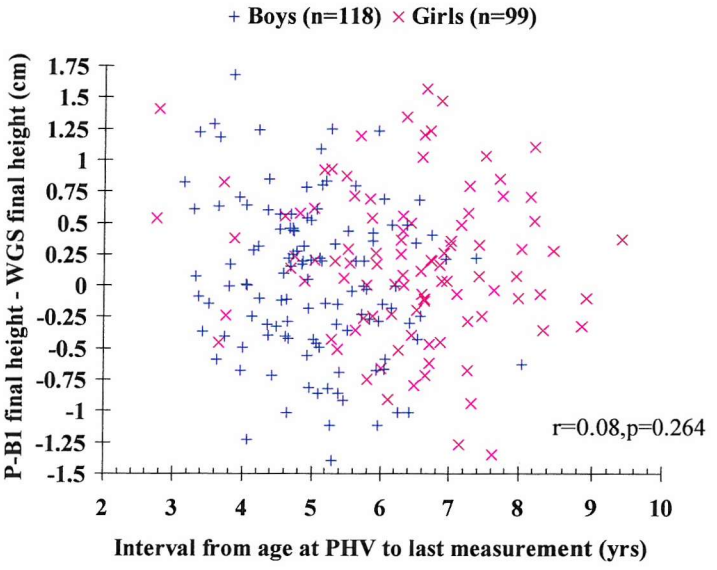


Figure 7.16 *The difference in estimates of final height between the P-B1 method and the WGS method in relation to time from PHV*

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APPENDIX A

Profile and growth data for Chapter 3

SHORT CHILDREN

ID	SEX	RECRUITMENT AGE(y)	RECRUITMENT HT(cm)	BIRTH CONDITIONS (1	2	3	4	5)	BONE AGE	TARGET HT(cm)	ASTHMA/ ECZEMA	HOME CONDITIONS (1	2	3)	HEIGHT(cm) AT 6YRS	9YRS
1	F	5.23	98.0	31.8	1870	35	2	Y	-1.60	155.8	N/N	IIIb^{U}	N	4	102.6	116.2
2	M	5.52	98.8	32.6	2920	38	2	N	-2.70	171.1	N/N	II	N	2	100.8	117.0
3	F	5.58	101.6	18.1	4465	40	2	N	-1.20	152.8	N/N	IV^{U}	N	4	103.9	118.8
4	F	6.51	105.7	17.2	3970	40	1	N	-.20	152.8	Y/N	IV^{U}	N	4	103.1	115.9
5	M	6.13	103.7	*	1430	33	1	N	-.60	170.9	N/N	II	N	1	103.4	118.6
6	F	5.67	102.1	30.0	3430	40	2	N	-2.20	156.2	N/N	II	N	3	103.9	120.8
7	F	5.46	99.9	25.3	2665	38	2	Y	*	150.9	N/N	II	N	2	103.3	120.6
8	F	5.65	100.7	*	3615	40	1	*	*	158.7	N/N	V	Y	3	102.0	119.3
9	F	5.91	103.1	23.6	3260	40	2	N	1.50	152.9	N/N	V	Y	2	104.0	119.3
10	F	5.79	101.6	17.9	3245	40	2	N	-1.00	154.9	Y/N	V^{U}	N	3	102.5	117.6
11	M	6.29	102.8	38.2	1360	32	4	N	.60	163.4	Y/N	V^{U}	N	13	101.1	117.9
12	F	5.96	100.3	23.1	2865	39	4	N	-.30	148.5	N/N	IV^{U}	N	4	100.4	116.2
13	F	5.56	100.6	19.6	2040	36	1	Y	-2.20	151.1	N/N	IV^{U}	N	2	102.7	116.3
14	F	5.78	102.7	24.3	3630	40	2	N	-.10	156.6	N/N	V^{U}	N	1	103.4	119.8
15	F	5.80	99.6	*	2695	38	2	*	-.70	161.6	Y/Y	II	N	2	*	*
16	F	6.14	102.2	*	3485	40	1	*	-1.10	156.3	N/N	II	N	3	101.2	116.2
17	M	5.59	99.5	27.8	1870	36	1	N	-.60	167.9	N/N	IIIa	N	2	101.4	115.2
18	F	5.88	103.1	21.1	3360	40	2	N	-1.40	154.9	N/N	IIIa	Y	3	104.8	124.5
19	F	5.41	100.5	28.2	3545	40	2	N	-.60	156.2	N/N	IIIa	N	3	104.1	117.7
20	M	5.48	101.7	24.4	3220	40	2	N	.30	168.3	N/N	IIIb	N	5	104.1	119.9
21	F	5.51	101.1	26.0	3445	40	2	N	-2.00	152.7	N/Y	V^{U}	N	3	104.0	121.4
22	F	5.31	99.5	23.1	2610	40	1	N	-.70	156.6	N/N	IIIb	N	2	103.6	119.9
23	M	5.50	101.1	27.6	3545	40	2	N	-1.00	175.6	Y/N	II	N	3	104.1	121.4
24	F	5.25	99.6	18.3	2155	40	1	N	.40	155.6	N/N	IV^{U}	N	2	104.4	119.7
25	F	6.07	102.4	19.5	2480	37	2	N	1.20	155.5	N/Y	IV	Y	3	102.1	117.5
26	M	6.35	104.2	33.7	3375	40	4	N	*	163.2	N/N	IIIb	N	4	102.4	117.0

BIRTH CONDITIONS: 1 maternal age, 2 weight(gm), 3 gestational age(wk), 4 order, 5 trauma
HOME CONDITIONS: 1 social class (^{U}=unemployed father), 2 single parent, 3 number siblings
MISSING DATA INDICATED BY *

SHORT CHILDREN

ID	SEX	RECRUITMENT AGE(y)	RECRUITMENT HT(cm)	BIRTH CONDITIONS (1	2	3	4	5)	BONE AGE	TARGET HT(cm)	ASTHMA/ ECZEMA	HOME CONDITIONS (1	2	3)	HEIGHT(cm) AT 6YRS	HEIGHT(cm) AT 9YRS
27	M	5.54	102.0	20.8	2295	39	2	N	.00	174.0	N/Y	IIIb	N	3	104.5	119.1
28	F	6.07	99.8	24.1	3330	40	1	Y	-1.50	153.2	N/N	IIIb	Y	1	99.9	114.4
29	F	6.01	103.8	23.0	2015	40	2	N	.60	152.3	N/N	IV	N	4	103.8	120.7
30	F	5.87	101.7	20.6	2225	40	1	Y	-2.10	150.4	Y/N	*	Y	2	102.2	118.9
31	M	5.59	94.1	16.8	3685	39	1	N	-2.60	166.8	N/N	IV^U	N	6	96.0	110.0
32	M	5.50	101.9	26.0	3315	40	2	N	-.50	164.7	N/N	*	Y	2	103.4	119.7
33	F	5.52	99.8	*	3035	36	1	*	.70	159.9	N/Y	V^U	Y	3	101.8	116.0
34	M	5.73	103.0	23.2	2580	40	4	N	*	160.9	N/N	V^U	N	4	104.6	119.8
35	M	6.07	102.2	*	2395	35	2	*	-.40	163.0	N/N	$IIIb^U$	N	4	102.0	117.7
36	F	5.53	99.1	31.0	2720	40	2	N	.60	147.7	N/N	IIIa	N	2	102.4	118.8
38	F	6.01	103.6	31.8	3460	40	2	N	-2.10	164.2	N/N	IIIa	N	3	103.9	120.3
39	M	6.19	101.2	*	1135	35	2	N	-.20	165.9	N/N	*	Y	3	100.1	116.4
40	M	5.70	99.6	19.9	2495	36	2	N	-.80	169.9	Y/Y	IIIb	N	3	101.7	114.9
41	F	6.27	103.1	26.4	2750	40	2	N	-1.10	158.7	N/N	IIIb	N	3	101.2	116.7
42	M	5.81	103.1	25.3	3005	40	2	N	.70	164.0	N/N	IIIb	N	2	104.3	122.7
46	M	5.65	96.3	*	2100	40	2	*	-1.70	172.9	Y/Y	*	Y	3	97.4	115.2
47	F	5.42	96.7	20.5	2535	37	2	N	-1.40	149.7	N/N	IIIb	N	3	100.0	115.9
48	F	5.47	97.0	*	2975	40	2	N	.10	161.4	N/N	II	N	3	100.3	113.8
49	F	6.02	103.3	28.6	3232	40	2	N	.30	159.8	N/N	II	N	3	103.1	119.4
50	M	5.23	97.9	25.3	*	*	4	N	-1.10	174.4	N/N	V	Y	8	102.3	120.5
51	M	5.43	101.2	27.2	3220	40	1	N	.70	160.7	N/N	IV	N	2	104.3	119.5
53	M	5.32	99.3	26.7	3655	40	2	N	-1.20	172.0	Y/N	IIIa	Y	3	102.9	116.6
54	F	5.99	102.2	22.5	2310	40	1	Y	*	156.0	N/N	*	N	5	102.6	119.3
55	F	6.29	103.0	*	3315	40	1		-1.00	155.1	N/N	II	N	1	101.4	115.9
59	F	6.11	104.0	22.8	2130	40	2	N	*	159.4	Y/Y	II	*	4	103.8	119.9
61	M	5.93	103.2	21.6	2765	39	1	N	-2.00	167.5	N/N	IV	N	2	103.7	119.2

BIRTH CONDITIONS: 1 maternal age, 2 weight(gm), 3 gestational age(wk), 4 order, 5 trauma
HOME CONDITIONS: 1 social class (^{U}=unemployed father), 2 single parent, 3 number siblings
MISSING DATA INDICATED BY *

SHORT CHILDREN

		RECRUITMENT		BIRTH CONDITIONS					BONE	TARGET	ASTHMA/	HOME CONDITIONS			HEIGHT(cm) AT	
ID	SEX	AGE(y)	HT(cm)	(1	2	3	4	5)	AGE	HT(cm)	ECZEMA	(1	2	3)	6YRS	9YRS
62	F	6.09	99.5	34.1	3755	40	2	N	.10	156.7	N/N	IIIb	N	3	99.7	115.9
63	M	5.56	102.6	22.0	2750	37	1	N	-.60	173.2	N/Y	I	N	2	105.2	121.0
64	M	5.53	100.5	25.6	3205	40	2	N	.10	167.5	N/N	IV^{U}	N	6	102.4	117.8
66	M	6.41	106.2	26.5	3970	40	2	N	-1.60	173.8	N/N	IIIb	Y	2	103.7	118.1
67	F	5.85	102.5	25.3	3020	40	1	N	-1.30	159.0	Y/Y	II	N	2	102.9	116.0
69	F	6.52	104.1	*	3645	40	2	*	-1.20	152.9	N/N	IIIb	Y	2	*	*
70	F	5.83	97.5	*	2395	38	2	N	-1.60	158.7	N/Y	V	N	4	98.7	114.8
71	M	5.92	101.2	*	2295	35	2	*	-.80	168.5	N/N	*	Y	3	101.8	119.9
72	M	6.19	105.5	28.8	3375	40	2	N	*	168.7	N/N	I	N	2	104.1	121.5
73	F	5.64	100.7	21.0	2750	40	2	N	-.90	155.7	N/N	IIIb^{U}	N	3	102.7	117.1
74	F	6.07	102.7	36.4	3400	40	2	N	-1.40	152.4	N/N	IIIb	N	2	102.7	117.0
75	F	5.28	98.1	23.4	2720	39	2	N	1.45	152.5	N/N	V	Y	3	101.6	115.4
76	M	5.66	102.4	26.7	2620	35	2	N	-.50	171.6	N/N	II	N	3	103.4	119.5
77	M	5.96	103.5	16.9	3230	40	1	N	-1.90	170.4	N/N	IIIb	Y	1	103.3	126.5
78	M	6.63	107.3	*	3515	40	2	N	*	159.4	*/*	IIIb	N	3	104.0	119.1
79	M	5.85	101.2	24.0	3910	40	2	N	1.60	169.1	N/N	V	N	2	102.9	118.0
80	M	5.45	96.5	31.9	2805	40	2	N	-.80	165.1	Y/Y	IIIb	N	3	99.6	116.5
81	F	5.51	99.8	*	2735	40	1	N	.90	152.8	N/N	IIIb	N	2	102.1	118.0
82	F	5.43	99.3	28.9	2255	34	1	Y	-1.40	157.4	Y/N	IIIb	N	1	102.3	118.1
83	F	5.84	97.7	22.5	1220	40	1	Y	.90	150.2	N/N	IV	N	1	98.7	115.4
85	M	5.88	103.5	24.7	3260	40	1	N	-.40	165.0	N/N	II	N	2	104.5	122.7
87	F	5.76	101.8	24.3	2110	40	1	Y	1.70	149.4	N/*	*	Y	2	103.5	120.7
88	M	5.45	101.1	31.1	3005	40	2	N	-1.40	170.8	N/Y	II	N	3	103.9	119.1
89	M	6.07	101.6	23.0	1985	38	4	Y	*	160.4	N/N	*	Y	4	101.1	115.9
90	M	6.07	101.9	23.0	2495	38	2	Y	*	160.4	N/N	*	Y	4	101.4	116.8
92	M	5.97	103.2	*	2355	37	2	*	.10	168.5	Y/N	V^{U}	N	4	104.3	119.6

BIRTH CONDITIONS: 1 maternal age, 2 weight(gm), 3 gestational age(wk), 4 order, 5 trauma
HOME CONDITIONS: 1 social class (^{U}=unemployed father), 2 single parent, 3 number siblings
MISSING DATA INDICATED BY *

SHORT CHILDREN

		RECRUITMENT		BIRTH CONDITIONS					BONE	TARGET	ASTHMA/	HOME CONDITIONS			HEIGHT(cm) AT	
ID	SEX	AGE(y)	HT(cm)	(1	2	3	4	5)	AGE	HT(cm)	ECZEMA	(1	2	3)	6YRS	9YRS
94	M	5.52	100.9	21.1	1475	32	1	N	-.10	160.3	N/N	*	Y	2	103.8	120.4
95	F	5.75	98.1	23.8	2565	40	1	N	-.70	157.3	N/N	IIIb	N	2	100.2	117.0
96	M	5.79	103.9	26.4	3075	38	1	Y	-.70	*	N/N	IIIb	Y	2	105.1	119.7
101	M	5.35	97.4	18.4	2665	38	2	Y	-1.20	168.8	N/N	II	Y	2	100.8	125.6
102	M	5.46	99.3	24.7	2255	37	1	N	-.70	165.5	N/N	IIIb	N	2	101.7	116.4
103	M	5.29	94.4	19.4	3290	40	2	N	-1.40	169.6	N/N	IIIa	Y	3	98.0	112.6
105	F	5.38	98.4	21.3	1730	32	2	N	-1.90	160.5	N/Y	IIIb^{U}	N	3	101.8	117.6
108	M	5.90	103.5	24.3	2440	38	1	N	1.20	171.9	N/N	IIIb	N	2	104.0	119.2
109	F	5.83	101.6	*	2835	40	2	*	*	153.8	N/N	IIIb	N	3	102.5	117.7
110	M	5.62	102.9	31.8	2635	40	1	Y	*	174.4	N/N	IIIb	N	1	105.5	124.1
111	M	4.95	95.1	*	2805	40	2	*	-.50	160.1	N/N	IIIb^{U}	N	2	*	*
112	F	5.10	96.5	35.2	3175	40	2	N	-1.80	152.4	N/N	IIIb	N	3	*	*
113	F	4.98	95.4	21.5	2495	40	2	Y	*	148.0	N/N	*	Y	2	100.8	119.0
114	M	5.38	99.9	26.3	3485	40	2	N	-.90	164.5	Y/N	IIIa	N	2	103.6	120.2
116	M	5.42	100.0	17.3	2850	40	1	N	*	165.0	N/N	IIIb	Y	2	102.9	117.4
118	M	5.59	94.8	21.8	3545	40	2	N	-2.58	166.8	N/N	IV^{U}	N	6	96.3	111.8
119	M	5.64	103.1	24.3	2920	40	1	N	*	169.0	*/*	IIIb	N	2	105.3	121.5
120	F	4.88	96.1	*	2665	40	1	*	.00	150.9	N/N	IIIb	N	2	*	*
121	F	5.32	97.1	31.4	3970	40	2	N	-1.60	153.5	N/Y	II	N	2	101.9	116.4
122	F	4.73	95.1	*	1445	34	1	*	-1.00	154.5	N/N	IV	N	1	*	*
123	M	4.84	97.5	*	3260	40	2	*	-1.00	173.4	N/N	IV	N	2	104.4	120.7
125	M	5.55	101.5	21.9	4155	38	2	Y	*	167.5	N/N	*	Y	2	104.3	120.2
126	M	5.61	101.6	*	*	*	*	*	*	*	*/*	*	*	*	*	*
128	M	5.25	100.2	22.5	3515	40	2	N	-.90	171.7	N/N	IIIb	N	3	104.2	120.1
130	F	5.03	95.9	*	2635	40	2	*	-1.30	160.5	Y/Y	II	N	3	101.8	118.5
131	M	5.47	99.9	20.5	2890	40	1	N	-.60	171.1	N/N	V	Y	4	103.0	119.9

BIRTH CONDITIONS: 1 maternal age, 2 weight(gm), 3 gestational age(wk), 4 order, 5 trauma
HOME CONDITIONS: 1 social class (^{U}=unemployed father), 2 single parent, 3 number siblings
MISSING DATA INDICATED BY *

SHORT CHILDREN

		RECRUITMENT		BIRTH CONDITIONS					BONE	TARGET	ASTHMA/	HOME CONDITIONS			HEIGHT(cm) AT	
ID	SEX	AGE(y)	HT(cm)	(1	2	3	4	5)	AGE	HT(cm)	ECZEMA	(1	2	3)	6YRS	9YRS
132	M	5.39	100.1	*	2665	40	2	N	-.90	170.4	N/N	IIIb	N	2	104.5	121.6
133	F	5.68	101.0	30.1	3205	40	2	N	-.70	164.1	N/N	II	N	3	102.2	117.9
134	M	5.46	99.5	20.5	3120	40	1	N	-1.90	163.2	N/N	IIIb	N	3	102.5	117.2
136	M	5.19	99.3	20.4	2735	37	2	Y	-.10	175.5	Y/Y	IIIa	N	3	105.2	123.8
137	F	5.38	99.3	21.9	2595	39	1	N	-.40	153.4	N/N	IV	N	2	102.8	119.3
138	F	4.96	97.2	19.7	2295	40	2	N	*	155.7	N/N	IIIb^{U}	N	3	102.2	119.6
139	F	5.31	97.9	30.3	3035	40	1	N	-.50	154.9	N/N	II	N	2	102.4	119.3
140	F	5.04	97.3	24.6	3655	40	2	N	*	154.4	N/N	IV	N	2	102.0	116.7
142	M	5.41	99.4	21.6	2295	40	1	N	-.10	169.8	N/N	IIIb	N	2	102.4	117.7
143	M	6.85	104.5	21.1	2820	40	1	N	-.55	166.3	N/N	IIIb	N	3	*	*
144	F	5.47	100.2	19.0	2865	40	1	N	1.10	*	N/N	IIIb^{U}	Y	2	103.0	117.8
145	M	5.04	96.6	29.4	2440	37	2	N	.00	165.7	N/N	IV	N	2	102.2	119.2
146	M	5.48	98.5	27.7	3460	40	2	N	-1.00	164.4	N/N	IIIb	N	2	102.0	119.2
147	M	5.31	98.2	24.8	3190	40	2	N	-.53	159.3	N/N	IIIb	N	2	*	*
148	M	5.28	101.0	24.8	3245	40	4	Y	-1.40	169.3	Y/N	IV	*	5	104.7	122.2
150	F	5.79	99.3	26.4	2805	40	2	N	.70	153.1	N/N	II	N	3	100.7	116.4
151	M	5.90	104.2	22.9	2040	36	1	Y	*	166.4	N/N	*	Y	1	104.0	118.5
152	F	5.35	99.5	21.7	2735	40	2	N	*	155.4	N/Y	IIIb	N	3	103.3	119.5
154	F	4.79	95.1	29.8	4165	40	2	Y	-1.80	155.7	N/N	*	N	3	102.9	120.2
155	M	5.20	98.0	29.4	2780	40	2	N	-1.20	170.9	Y/Y	IV	N	3	102.6	114.8
156	F	5.47	100.8	*	2906	40	2	N	*	147.2	*/*	IIIb	N	3	103.2	116.8
158	M	5.56	100.6	27.8	3245	40	1	N	-2.20	172.4	N/N	*	*	2	103.2	118.8
159	F	5.12	98.0	21.1	2865	38	2	Y	-.30	165.6	N/Y	IIIb	N	3	103.3	120.7
160	M	5.01	97.9	27.0	2805	40	4	N	-1.10	175.6	Y/Y	IV	N	6	103.5	118.8
161	M	5.73	101.4	27.4	1870	34	2	Y	-.40	*	Y/N	*	*	*	104.3	121.2
163	M	5.16	98.8	23.7	3600	40	1	Y	-1.60	172.0	N/N	IIIb	Y	1	104.0	119.6

BIRTH CONDITIONS: 1 maternal age, 2 weight(gm), 3 gestational age(wk), 4 order, 5 trauma
HOME CONDITIONS: 1 social class (^{U}=unemployed father), 2 single parent, 3 number siblings
MISSING DATA INDICATED BY *

SHORT CHILDREN

ID	SEX	RECRUITMENT AGE(y)	RECRUITMENT HT(cm)	BIRTH CONDITIONS (1	2	3	4	5)	BONE AGE	TARGET HT(cm)	ASTHMA/ ECZEMA	HOME CONDITIONS (1	2	3)	HEIGHT(cm) AT 6YRS	HEIGHT(cm) AT 9YRS
164	M	4.90	98.4	24.9	3175	40	2	N	-1.40	162.1	Y/Y	V^U	N	3	103.8	121.2
165	M	5.65	102.2	32.3	3290	40	2	N	-.50	171.5	N/Y	*	Y	2	104.1	120.3
168	F	5.35	96.3	22.4	3430	40	2	N	-.70	152.5	N/Y	IIIa	N	2	99.6	112.9
169	M	5.61	101.7	22.5	2850	39	1	N	-.70	173.8	N/N	IV	Y	2	103.9	119.0
170	M	5.23	100.2	26.3	3175	40	1	N	.30	162.0	N/N	IIIb	N	2	104.0	119.0
171	M	5.56	102.7	*	2780	40	2	*	-.20	*	N/N	IV	Y	2	*	*
172	M	5.52	100.7	34.7	1615	38	1	Y	.50	166.6	N/N	IIIb	N	2	103.4	118.8
173	M	5.56	102.5	*	2270	*	4	*	-1.50	164.3	Y/Y	IIIb	N	7	*	*
175	M	5.11	96.7	22.9	3245	40	1	N	-1.20	167.4	N/N	IIIb	N	3	100.9	113.5
177	M	4.82	93.8	27.2	3315	38	1	Y	-1.95	161.7	Y/Y	I	N	2	99.9	115.1

BIRTH CONDITIONS: 1 maternal age, 2 weight(gm), 3 gestational age(wk), 4 order, 5 trauma
HOME CONDITIONS: 1 social class (^{U}=unemployed father), 2 single parent, 3 number siblings
MISSING DATA INDICATED BY *

CONTROL CHILDREN

ID	SEX	RECRUITMENT AGE(y)	RECRUITMENT HT(cm)	BIRTH CONDITIONS (1	2	3	4	5)	BONE AGE	TARGET HT(cm)	ASTHMA/ ECZEMA	HOME CONDITIONS (1	2	3)	HEIGHT(cm) AT 6YRS	HEIGHT(cm) AT 9YRS
201	F	5.75	114.4	*	3685	40	2	*	*	165.6	N/N	II	N	2	*	*
202	M	5.90	114.7	18.7	4080	40	1	Y	*	179.1	N/N	IIIb	Y	2	115.7	134.0
203	F	5.86	108.2	*	3855	40	2	*	*	153.8	N/N	IIIb	N	4	109.5	125.8
204	F	7.00	121.6	23.8	2580	40	1	N	*	165.5	N/N	II	N	2	*	*
205	M	7.14	123.3	23.7	3570	40	2	N	*	171.6	N/N	IV	N	2	*	*
206	F	6.05	117.1	26.5	3390	40	2	N	*	163.2	N/N	IIIb	N	3	117.3	133.9
207	F	5.83	111.1	32.3	3175	40	2	N	*	160.9	N/N	II	N	3	112.4	130.5
208	F	6.21	112.3	20.9	3315	40	1	N	*	160.4	N/N	IIIb	N	2	111.2	129.5
209	F	6.48	118.4	35.0	*	*	2	N	*	156.4	*/*	IV	N	3	115.9	133.1
210	F	6.19	119.0	23.4	3515	40	2	N	*	164.1	N/N	IIIb	N	2	117.8	137.4
211	M	6.15	112.6	*	3345	38	2	*	*	170.8	N/N	IIIb	N	2	111.5	125.8
212	F	8.49	127.2	26.1	3345	40	2	N	*	160.5	N/N	II	Y	2	*	*
213	F	6.03	113.2	19.6	2880	40	1	N	*	161.3	N/N	IV	Y	2	112.6	130.0
214	F	6.32	112.6	27.3	2780	40	2	N	*	160.5	N/N	*	Y	3	110.1	128.4
215	F	6.44	115.2	*	3400	40	1	*	*	160.8	N/N	IIIa	N	3	*	*
216	F	6.69	116.8	31.9	3345	36	2	N	*	173.4	N/N	IIIb	N	3	112.8	129.3
217	M	6.09	115.6	*	3630	40	2	*	*	171.9	N/N	I	N	3	115.2	133.5
218	F	6.21	113.6	*	3230	37	2	*	*	166.4	N/N	IIIb	Y	5	112.3	129.2
219	F	5.87	115.9	31.8	3740	40	1	N	*	168.8	N/N	II	Y	2	117.0	135.2
220	M	5.99	111.9	30.7	3515	40	2	N	*	170.4	N/N	I	N	2	112.0	130.2
221	F	5.95	116.7	24.6	3615	40	2	N	*	167.6	N/N	II	N	2	117.4	136.2
222	F	5.84	111.8	20.2	2480	40	1	Y	*	160.5	N/N	V^U	N	4	113.2	127.2
223	M	6.00	122.0	26.5	3910	38	1	N	*	184.0	N/N	IIIa	N	2	122.3	142.1
224	F	5.76	109.1	17.9	3400	40	1	N	*	157.6	N/N	*	Y	2	110.4	127.4
225	F	6.53	114.3	26.3	2835	37	1	Y	*	161.7	N/N	II^U	Y	2	111.8	128.2
226	M	6.36	122.3	24.1	4000	40	1	N	*	181.3	N/N	II	N	2	119.9	137.8

BIRTH CONDITIONS: 1 maternal age, 2 weight(gm), 3 gestational age(wk), 4 order, 5 trauma
HOME CONDITIONS: 1 social class (^{U}=unemployed father), 2 single parent, 3 number siblings
MISSING DATA INDICATED BY *

CONTROL CHILDREN

ID	SEX	RECRUITMENT AGE(y)	RECRUITMENT HT(cm)	BIRTH CONDITIONS (1	2	3	4	5)	BONE AGE	TARGET HT(cm)	ASTHMA/ ECZEMA	HOME CONDITIONS (1	2	3)	HEIGHT(cm) AT 6YRS	HEIGHT(cm) AT 9YRS
227	M	6.17	116.5	*	4025	40	2	N	*	178.7	N/N	IV	N	3	115.6	132.9
228	F	6.56	115.9	*	2410	40	4	N	*	154.8	N/N	II^U	N	3	112.4	131.4
229	F	6.53	118.7	28.0	3035	40	1	N	*	157.9	N/N	IIIb	N	1	115.4	133.3
230	F	6.24	115.3	*	3740	40	2	*	*	166.5	N/N	I	N	4	113.6	130.7
231	M	6.12	121.2	31.5	3135	40	2	N	*	178.2	Y/N	II	N	2	120.7	139.7
232	M	5.83	116.8	22.1	*	40	2	N	*	*	N/N	*	*	2	118.1	138.0
233	F	6.08	113.1	28.1	2325	36	4	Y	*	160.5	Y/N	IIIb	N	4	113.1	128.3
234	M	6.21	116.4	21.2	3245	38	2	N	*	173.5	Y/N	IV	N	2	115.4	131.4
235	M	6.69	120.6	16.3	2920	40	1	N	*	*	N/N	*	Y	3	116.4	132.4
236	F	6.08	112.1	29.1	2780	39	2	N	*	160.4	N/N	IIIb	N	4	113.3	131.0
238	F	6.48	120.9	*	4090	40	2	*	*	163.5	N/N	IIIa	N	2	118.7	137.2
239	M	6.65	120.6	32.0	3145	38	2	N	*	183.4	N/N	I	N	2	116.3	134.7
240	M	6.19	116.9	24.9	3985	39	2	N	*	178.0	N/N	IIIa	N	2	115.5	134.1
241	F	6.73	121.7	23.5	2610	35	2	N	*	166.1	N/N	IIIb	N	3	116.9	136.6
242	M	6.17	112.1	22.4	4000	40	1	Y	*	169.4	N/N	IIIb	N	2	111.2	131.7
246	M	6.51	120.4	22.3	3400	40	2	N	*	182.8	N/N	IV	Y	3	116.9	136.4
247	F	5.81	112.9	29.3	2920	39	1	N	*	161.2	N/N	IIIb	N	2	114.1	131.1
248	F	5.88	109.4	28.1	3545	40	1	N	*	161.0	N/N	I	N	2	109.9	126.7
249	F	6.50	113.2	27.6	3500	40	1	N	*	160.9	N/N	I	N	2	110.4	126.5
250	M	6.13	112.1	24.3	3740	40	2	N	*	180.2	N/N	IIIb	N	3	112.0	129.4
251	M	6.15	117.6	*	4140	40	1	*	*	*	N/N	*	Y	1	116.8	135.4
253	M	5.82	117.4	25.8	3815	39	2	N	*	171.0	N/N	IIIa	N	2	118.0	138.4
254	F	6.54	117.1	24.1	3005	40	1	Y	*	169.1	N/N	IIIb	N	3	113.8	131.1
255	F	6.71	116.6	*	2780	34	2	N	*	162.5	N/N	IIIb	N	3	112.1	129.2
259	F	6.40	114.1	28.9	3685	39	2	N	*	155.1	N/N	*	N	2	112.5	127.7
260	M	6.15	112.9	*	3290	40	*	*	*	*	*/*	*	*	*	112.0	128.6

BIRTH CONDITIONS: 1 maternal age, 2 weight(gm), 3 gestational age(wk), 4 order, 5 trauma
HOME CONDITIONS: 1 social class (^{U}=unemployed father), 2 single parent, 3 number siblings
MISSING DATA INDICATED BY *

CONTROL CHILDREN

		RECRUITMENT		BIRTH CONDITIONS					BONE	TARGET	ASTHMA/	HOME CONDITIONS			HEIGHT(cm) AT	
ID	SEX	AGE(y)	HT(cm)	(1	2	3	4	5)	AGE	HT(cm)	ECZEMA	(1	2	3)	6YRS	9YRS
261	M	6.44	119.0	22.7	3030	40	1	N	*	173.4	N/N	IIIb	N	2	116.3	136.3
262	F	6.60	116.3	*	3855	39	2	Y	*	*	N/N	II	Y	2	112.6	130.4
263	M	5.96	113.2	21.7	2720	34	2	Y	*	175.2	N/N	*	Y	2	113.8	131.1
264	M	6.22	112.1	*	2495	40	2	*	*	175.7	N/Y	*	N	3	*	*
266	M	6.77	119.2	27.0	2595	40	1	N	*	174.0	N/N	II	N	3	*	*
267	F	6.41	117.6	28.2	3430	40	1	N	*	167.6	*/*	IIIa	Y	1	115.6	131.9
269	F	7.10	122.3	25.9	3855	40	1	N	*	162.7	N/N	II	Y	1	*	*
270	F	6.48	113.0	19.4	3075	38	2	N	*	162.6	N/N	IIIb^{U}	N	2	109.7	128.7
271	M	6.58	117.1	21.5	3800	40	1	N	*	179.6	N/N	I	N	3	113.3	132.4
272	M	6.68	122.2	28.9	3825	40	2	N	*	174.7	N/N	IIIa	N	2	117.6	135.4
273	F	6.27	116.3	20.9	3290	40	1	N	*	168.8	N/N	IIIb	Y	2	114.9	134.1
274	F	6.22	110.8	21.4	3390	36	1	N	*	161.3	N/N	IIIa	N	2	109.3	127.7
275	F	5.79	108.7	*	2580	36	1	N	*	164.0	N/Y	IIIb^{U}	N	2	110.4	126.2
276	M	5.99	120.6	29.7	3955	40	2	N	*	176.7	N/N	IIIa	N	2	121.0	138.0
277	M	6.45	118.0	23.0	3685	40	2	N	*	175.5	N/N	IV^{U}	N	3	115.6	133.6
278	M	6.64	119.9	23.8	4180	40	1	N	*	187.0	N/N	IIIb	N	2	115.6	133.4
279	M	6.49	111.6	23.0	3230	38	2	N	*	177.4	N/N	IV	N	2	108.9	125.9
280	M	6.05	111.0	26.1	2805	40	1	N	*	174.8	N/N	II	N	1	110.5	125.2
281	F	6.04	115.9	36.1	2950	40	2	N	*	166.4	N/N	II	N	3	115.8	136.4
282	F	6.07	114.1	25.7	2720	40	2	N	*	166.1	Y/Y	*	N	2	113.7	135.1
283	F	6.32	112.2	25.2	2580	40	2	N	*	164.4	N/N	IIIb	N	2	110.1	126.1
285	M	6.34	118.1	22.8	4265	40	2	N	*	181.4	N/N	IV	N	3	116.4	132.5
287	F	6.19	111.8	21.7	3090	40	1	N	*	160.5	N/N	IIIb	Y	2	110.9	127.7
288	M	6.10	119.2	18.9	3005	40	1	N	*	174.6	N/N	IIIb	N	2	118.4	135.5
289	M	6.63	119.0	*	3290	40	1	*	*	183.7	N/N	IIIa	N	1	*	*
290	M	6.66	117.7	22.5	3485	39	1	N	*	185.4	N/N	IIIb	N	2	113.7	131.0

BIRTH CONDITIONS: 1 maternal age, 2 weight(gm), 3 gestational age(wk), 4 order, 5 trauma
HOME CONDITIONS: 1 social class (^{U}=unemployed father), 2 single parent, 3 number siblings
MISSING DATA INDICATED BY *

CONTROL CHILDREN

		RECRUITMENT		BIRTH CONDITIONS					BONE	TARGET	ASTHMA/	HOME CONDITIONS			HEIGHT(cm) AT	
ID	SEX	AGE(y)	HT(cm)	(1	2	3	4	5)	AGE	HT(cm)	ECZEMA	(1	2	3)	6YRS	9YRS
291	M	6.70	121.1	23.1	4225	40	1	N	*	178.9	N/N	*	Y	2	117.1	135.3
292	M	6.51	117.6	17.6	3205	40	1	N	*	179.7	N/N	*	N	2	114.1	133.4
294	M	8.56	129.6	27.1	3289	40	2	*	*	179.7	N/N	IIIa	N	3	*	*
295	F	6.20	115.5	26.9	2975	40	1	N	*	164.8	N/N	IIIb	N	3	114.6	133.8
296	M	6.28	113.6	21.4	3005	40	2	N	*	168.1	N/N	IIIb^{U}	N	4	111.7	129.4
301	M	5.80	111.8	29.4	2085	35	1	N	*	175.2	Y/N	IIIb	N	2	113.2	129.6
302	M	5.50	113.5	19.5	3005	40	1	N	*	175.0	N/N	IIIb	Y	1	116.9	134.6
303	M	5.54	118.7	19.4	3005	38	1	N	*	180.0	N/N	II	N	2	120.4	136.5
305	F	5.89	115.8	25.5	3260	40	4	N	*	155.4	N/N	IIIa	*	4	116.8	133.6
308	M	5.96	116.4	27.3	4055	40	2	N	*	178.5	N/N	II	N	3	116.0	133.9
309	F	5.82	113.9	*	2440	37	1	N	*	161.7	N/N	II	Y	2	114.5	134.3
310	M	5.55	111.5	27.4	3570	38	1	Y	*	177.4	N/N	II	N	3	115.0	131.6
312	F	5.06	104.8	23.1	2805	40	1	N	*	161.3	N/N	IIIb	Y	3	111.2	129.3
313	F	5.46	107.4	27.6	3220	40	2	N	*	152.6	N/N	IV	Y	3	110.6	126.3
314	M	5.38	106.0	33.3	2920	38	2	N	*	179.9	N/N	II	N	3	111.2	128.2
316	M	5.44	111.6	32.3	3530	40	2	N	*	175.4	*/*	IIIb	*	3	115.4	134.9
319	M	5.65	109.5	19.6	3260	40	1	N	*	172.1	N/N	IIIb	N	1	112.0	127.9
320	F	5.18	109.2	*	3415	40	2	*	*	*	N/N	IIIb	N	3	115.7	133.8
321	F	5.27	107.0	30.4	3560	40	2	N	*	157.5	N/N	IIIa	N	4	112.3	130.0
322	F	4.95	102.7	23.3	3245	40	2	N	*	161.7	N/Y	IIIb	Y	2	109.5	127.4
323	M	5.33	113.7	23.8	3600	39	2	N	*	183.5	N/N	IIIb	N	4	118.2	135.3
324	M	5.28	104.1	21.8	3600	38	2	N	*	174.5	N/N	V	N	4	108.1	124.6
325	M	5.27	117.1	*	*	*	*	*	*	*	*/*	*	*	*	*	*
328	M	5.22	112.3	27.5	3090	40	2	N	*	181.1	N/N	IIIb	N	2	117.6	139.2
330	F	5.08	107.8	33.1	3855	38	1	N	*	164.6	N/N	IIIb	N	2	115.8	135.5
331	M	6.24	115.7	*	3005	40	2	*	*	178.6	N/N	IIIb^{U}	N	3	*	*

BIRTH CONDITIONS: 1 maternal age, 2 weight(gm), 3 gestational age(wk), 4 order, 5 trauma
HOME CONDITIONS: 1 social class (^{U}=unemployed father), 2 single parent, 3 number siblings
MISSING DATA INDICATED BY *

CONTROL CHILDREN

		RECRUITMENT		BIRTH CONDITIONS					BONE	TARGET	ASTHMA/	HOME CONDITIONS			HEIGHT(cm) AT	
ID	SEX	AGE(y)	HT(cm)	(1	2	3	4	5)	AGE	HT(cm)	ECZEMA	(1	2	3)	6YRS	9YRS
332	M	5.34	107.6	21.7	2920	40	1	N	*	179.9	N/N	IIIb	N	3	111.8	127.1
333	F	5.62	111.8	21.2	2850	40	2	N	*	160.2	N/N	IV^{U}	Y	1	114.1	131.2
334	M	5.47	113.0	27.2	3870	40	2	N	*	177.7	N/N	II	N	2	116.6	136.4
336	M	5.37	110.7	19.6	3416	40	1	N	*	174.0	*/*	V	Y	2	114.8	130.3
337	F	5.55	112.3	*	3515	40	1	*	*	163.0	N/N	IIIb	N	2	115.2	131.7
338	F	5.54	114.9	19.4	3969	40	1	N	*	*	*/*	IIIb	N	4	116.9	133.2
339	F	5.37	114.5	*	3545	40	2	*	*	164.2	N/N	IIIa	N	4	*	*
340	F	5.00	109.5	23.6	2865	40	1	N	*	167.8	N/N	IIIb	N	2	115.4	133.6
342	M	5.39	112.6	*	3415	40	2	*	*	181.2	N/N	IIIb	N	2	116.1	132.7
343	M	7.94	128.9	*	3629	40	4	*	*	*	*/*	*	*	*	*	*
344	F	5.44	112.3	*	3630	38	2	*	*	168.6	N/N	II	N	2	116.3	133.4
346	M	5.49	109.5	24.7	2920	37	1	N	*	177.4	Y/N	IIIb	N	2	111.5	129.0
347	M	6.35	121.1	30.7	4200	38	2	N	*	177.0	N/N	IIIb	N	2	119.3	136.8
348	M	5.38	115.9	34.2	3885	36	2	N	*	177.9	N/N	I	N	2	120.0	139.3
350	F	7.80	124.3	29.4	3630	40	1	N	*	160.2	N/N	II	N	2	*	*
351	M	5.86	120.1	17.8	3870	40	1	N	*	177.6	N/N	IIIa	N	2	121.3	140.9
352	F	5.27	106.4	26.4	3020	38	4	Y	*	163.0	N/N	IIIb	Y	6	110.4	125.9
354	F	4.87	103.3	25.2	2055	34	2	Y	*	*	N/N	*	Y	3	110.7	128.8
355	M	5.74	117.6	27.4	4090	40	2	N	*	183.2	N/N	IIIb	N	3	119.7	139.5
356	F	5.59	115.1	17.3	3050	40	1	N	*	170.5	Y/N	IV	N	1	118.2	140.7
358	M	6.05	112.8	23.8	2890	40	1	N	*	172.7	N/N	II	N	1	112.9	128.7
359	F	5.77	112.3	25.9	3375	38	1	N	*	160.8	N/N	I	Y	2	114.3	133.0
360	M	5.00	105.2	28.1	2805	36	4	Y	*	175.9	N/N	II	N	4	111.6	130.3
361	M	5.79	117.1	22.8	3230	40	1	N	*	182.0	N/N	IV	N	2	118.8	138.0
363	M	5.16	107.8	21.0	3515	36	1	Y	*	178.6	N/N	II	N	2	113.2	131.4
364	M	5.29	109.8	26.9	2650	40	1	N	*	177.8	N/N	IIIb	N	2	113.2	130.7

BIRTH CONDITIONS: 1 maternal age, 2 weight(gm), 3 gestational age(wk), 4 order, 5 trauma
HOME CONDITIONS: 1 social class (^{U}=unemployed father), 2 single parent, 3 number siblings
MISSING DATA INDICATED BY *

CONTROL CHILDREN

ID	SEX	RECRUITMENT AGE(y)	RECRUITMENT HT(cm)	BIRTH CONDITIONS (1	2	3	4	5)	BONE AGE	TARGET HT(cm)	ASTHMA/ ECZEMA	HOME CONDITIONS (1	2	3)	HEIGHT(cm) AT 6YRS	HEIGHT(cm) AT 9YRS
365	M	5.66	114.5	23.5	3260	40	2	N	*	177.8	N/N	IIIb	N	2	115.7	133.3
368	F	5.80	113.6	20.9	3290	40	1	Y	*	162.4	N/N	IIIb	N	2	115.0	133.4
369	M	5.48	109.6	32.9	2950	40	4	Y	*	182.1	Y/Y	II	N	5	112.8	132.2
370	M	5.66	117.5	27.4	4140	40	2	N	*	179.0	N/N	IIIa	N	2	120.0	138.4
371	M	5.69	117.5	21.5	3770	40	1	N	*	172.5	N/N	IIIb	N	3	119.9	137.0
372	M	5.65	115.5	16.5	3660	40	1	N	*	183.5	N/N	IV	Y	1	116.9	136.0
373	M	5.53	115.6	21.1	3375	38	1	N	*	176.8	N/N	IIIb	N	1	117.0	133.5
375	M	5.49	116.9	24.6	4750	35	2	N	*	*	N/Y	IIIb	Y	2	119.4	138.3
376	M	6.08	115.9	22.3	3630	40	1	N	*	175.2	N/N	IIIb	N	2	115.6	134.3
377	M	5.29	114.4	*	4080	40	*	*	*	*	*/*	*	*	*	119.3	138.5

BIRTH CONDITIONS: 1 maternal age, 2 weight(gm), 3 gestational age(wk), 4 order, 5 trauma
HOME CONDITIONS: 1 social class (^{U}=unemployed father), 2 single parent, 3 number siblings
MISSING DATA INDICATED BY *

APPENDIX B

Pubertal growth data for Chapter 4

SHORT CHILDREN

ID	SEX	ATOPY 1	ATOPY 2	SOCIAL CLASS	---PREPUBERTAL---- HT(cm)	WT(kg)	BMI	--TAKE-OFF-- AGE(y)	HT(cm)	PUBERTAL PEAK AGE(y)	cm/y	-COMPLETION- AGE(Y)	HT(cm)	MENARCHE AGE(Y)
3	F	N	N	C2	114.2	21.6	16.56	10.19	123.5	12.45	7.50	14.71	149.3	13.64
4	F	Y	Y	C2	112.3	20.7	16.43	11.12	123.1	13.84	6.82	15.87	146.9	15.76
5	M	N	N	A	113.9	18.4	14.22	11.18	130.0	13.71	11.16	15.79	162.0	*
6	F	N	N	B	115.4	21.8	16.33	9.27	122.3	12.65	7.56	14.84	152.1	13.78
7	F	Y	N	C1	115.3	18.9	14.23	8.90	119.6	10.95	8.20	14.06	151.0	12.97
8	F	Y	N	*	113.6	19.8	15.37	9.11	120.3	11.47	7.91	13.82	149.3	12.92
9	F	Y	N	E	114.4	23.4	17.90	8.39	116.3	11.56	9.02	13.43	145.2	12.08
10	F	Y	Y	D	112.6	21.0	16.56	9.47	119.9	11.95	9.29	13.64	146.6	12.76
11	M	Y	N	E	113.0	19.1	14.98	8.81	116.8	12.90	10.25	15.31	159.6	*
14	F	N	N	C2	114.8	21.3	16.13	10.80	130.3	12.29	8.20	14.22	150.0	13.92
16	F	N	N	*	111.5	18.3	14.72	*	*	*	*	*	*	12.42
18	F	N	N	E	118.6	18.0	12.79	*	*	*	*	*	*	14.16
19	F	N	N	A	113.5	20.8	16.18	*	*	*	*	*	*	12.24
20	M	N	N	C2	115.0	20.3	15.39	12.08	134.0	15.09	7.71	16.66	161.2	*
21	F	Y	N	D	116.1	29.4	21.81	8.95	120.9	11.81	8.33	14.02	148.3	12.78
22	F	N	N	C2	114.8	19.6	14.87	8.32	116.5	10.93	7.48	13.32	146.4	12.47
23	M	Y	N	B	115.9	20.9	15.58	12.94	140.5	14.92	11.56	17.12	169.2	*
24	F	Y	N	D	114.5	17.3	13.17	8.66	118.4	10.70	8.24	13.24	145.0	12.49
26	M	N	N	D	112.4	17.7	14.00	11.91	130.5	15.23	8.01	18.51	162.9	*
27	M	N	Y	C2	114.5	19.5	14.87	13.54	138.9	15.79	7.52	17.77	163.6	*
28	F	Y	N	D	109.9	18.7	15.48	9.22	115.4	12.44	7.98	14.19	143.0	13.50
29	F	N	N	D	115.5	19.5	14.62	9.60	123.1	13.24	8.89	15.13	156.2	14.06
30	F	Y	N	E	113.1	15.5	12.12	9.36	119.8	12.01	9.29	13.85	148.8	14.99
32	M	N	N	D	115.1	17.5	13.17	13.02	136.8	16.15	9.22	18.22	167.6	*
33	F	Y	N	D	112.0	18.0	14.38	9.97	119.7	13.03	7.92	15.48	149.4	14.86
34	M	N	N	D	114.5	18.9	14.45	11.35	131.0	13.74	8.98	16.63	160.1	*
36	F	N	N	B	113.3	18.6	14.52	11.56	130.5	12.96	7.69	14.59	145.5	13.20

ATOPY: 1 one or more atopic condition (I.e. asthma, hayfever, allergy, or eczema), 2 steriod treatment
MISSING DATA INDICATED BY *

SHORT CHILDREN

		ATOPY		SOCIAL	---PREPUBERTAL----			--TAKE-OFF--		PUBERTAL PEAK		-COMPLETION-		MENARCHE
ID	SEX	1	2	CLASS	HT(cm)	WT(kg)	BMI	AGE(y)	HT(cm)	AGE(y)	cm/y	AGE(Y)	HT(cm)	AGE(Y)
38	F	N	N	C1	114.6	19.0	14.43	8.99	120.6	12.00	9.40	13.96	151.4	13.14
39	M	N	N	E	110.8	16.8	13.68	10.02	121.4	13.26	9.56	16.35	162.5	*
40	M	Y	Y	E	110.6	17.8	14.56	10.10	119.5	13.51	10.59	16.20	154.8	*
41	F	N	Y	C2	111.5	20.1	16.15	10.56	126.1	12.04	8.68	14.04	148.1	13.43
42	M	N	N	C1	116.9	19.7	14.44	13.18	147.1	14.77	7.72	17.25	168.8	*
46	M	Y	N	*	109.5	16.6	13.86	12.19	131.3	15.10	10.25	*	*	*
47	F	Y	N	D	111.0	17.0	13.80	9.42	117.9	11.50	8.24	13.43	140.9	12.17
48	F	N	N	C1	110.0	18.9	15.61	10.28	119.0	12.21	7.55	14.30	142.0	13.19
49	F	Y	Y	C1	114.2	19.4	14.87	10.98	127.6	13.23	6.57	14.98	148.4	14.15
50	M	Y	Y	D	114.6	19.8	15.04	10.81	129.6	13.98	12.10	16.47	168.2	*
51	M	Y	N	D	114.9	22.3	16.92	9.88	123.7	12.93	10.84	14.87	155.3	*
53	M	Y	Y	B	112.5	19.4	15.35	11.33	126.7	14.95	9.66	17.87	164.4	*
54	F	N	N	E	114.4	19.9	15.21	10.08	122.9	13.15	8.84	15.03	148.4	13.59
59	F	Y	Y	C2	114.9	18.4	13.95	9.68	123.1	12.95	7.84	15.03	153.7	14.36
61	M	N	N	D	114.3	20.1	15.37	12.49	137.4	14.28	9.79	16.30	164.4	*
63	M	N	N	A	116.4	18.6	13.73	11.51	133.8	14.37	9.88	16.11	161.2	*
64	M	N	N	E	112.8	20.6	16.21	11.75	132.6	13.85	8.70	15.84	158.3	*
67	F	Y	Y	B	112.0	19.0	15.16	9.76	119.8	12.26	7.40	14.76	146.3	13.50
70	F	Y	N	D	109.7	18.1	15.05	10.86	122.7	12.87	8.06	14.79	143.9	14.43
71	M	N	N	C2	114.1	20.2	15.51	12.91	139.2	14.53	9.39	16.83	164.0	*
72	M	N	N	B	115.8	20.0	14.95	11.70	134.9	14.47	10.00	16.75	167.4	*
73	F	N	N	C2	112.5	18.9	14.92	9.16	118.0	11.29	8.51	13.61	145.5	12.47
74	F	N	N	C2	112.2	17.4	13.81	11.14	127.5	12.94	9.72	15.20	152.1	13.70
76	M	N	N	B	114.0	19.4	14.89	11.63	130.6	15.66	11.90	18.11	167.8	*
77	M	Y	N	D	118.6	23.3	16.59	12.44	147.6	14.44	9.67	16.56	173.9	*
78	M	Y	N	D	114.4	21.5	16.41	10.15	124.2	13.43	10.67	15.68	160.3	*
79	M	N	N	C2	113.2	22.6	17.61	14.37	139.0	15.79	8.41	17.22	154.5	*

ATOPY: 1 one or more atopic condition (I.e. asthma, hayfever, allergy, or eczema), 2 steriod treatment
MISSING DATA INDICATED BY *

SHORT CHILDREN

		ATOPY		SOCIAL	---PREPUBERTAL----			--TAKE-OFF--		PUBERTAL PEAK		-COMPLETION-		MENARCHE
ID	SEX	1	2	CLASS	HT(cm)	WT(kg)	BMI	AGE(y)	HT(cm)	AGE(y)	cm/y	AGE(Y)	HT(cm)	AGE(Y)
85	M	Y	Y	B	117.3	24.4	17.76	12.36	136.1	14.24	8.54	16.39	156.6	*
87	F	N	N	D	115.2	21.9	16.52	8.65	118.7	10.57	7.01	12.66	142.1	12.42
89	M	N	N	D	111.2	18.9	15.33	10.51	122.7	13.79	9.04	16.02	155.9	*
90	M	N	N	D	111.7	19.4	15.59	11.03	126.7	14.13	9.49	16.02	158.5	*
94	M	Y	Y	C2	115.6	20.1	15.00	12.50	137.0	14.18	9.38	16.72	160.5	*
95	F	Y	Y	C2	111.8	15.6	12.48	11.84	128.8	13.29	6.88	16.26	149.4	16.64
96	M	N	N	D	115.2	21.4	16.14	13.71	138.6	16.00	6.94	18.87	164.1	*
101	M	N	N	A	118.0	22.0	15.83	11.80	138.5	13.49	11.54	16.38	166.0	*
102	M	N	N	C2	111.8	18.4	14.72	12.14	131.7	14.47	8.97	16.80	158.9	*
103	M	N	N	C2	109.2	14.9	12.49	13.72	131.9	16.01	10.50	18.25	159.6	*
105	F	Y	N	C1	112.5	17.2	13.60	10.12	122.6	12.42	7.79	14.63	147.5	13.57
108	M	N	N	C1	114.7	19.2	14.60	11.32	129.3	14.58	7.92	16.39	157.9	*
110	M	N	N	D	118.1	21.8	15.67	11.13	134.1	13.93	6.75	16.20	161.2	*
113	F	N	N	C2	113.1	20.7	16.15	9.60	121.7	12.29	8.60	14.08	149.0	13.17
114	M	Y	Y	C2	114.7	24.5	18.61	10.83	128.6	13.81	8.81	15.81	157.1	*
116	M	N	N	C2	113.1	19.4	15.19	12.21	131.3	15.59	10.64	17.93	164.7	*
118	M	N	N	E	107.0	16.3	14.25	13.68	130.4	16.55	11.94	19.17	161.9	*
119	M	N	N	C1	116.3	21.2	15.68	10.64	129.4	13.88	9.79	15.83	161.7	*
121	F	N	N	A	111.9	17.0	13.57	8.20	113.0	11.72	8.11	14.18	149.0	13.13
123	M	Y	N	*	115.7	20.8	15.57	13.27	137.2	15.36	8.77	*	*	*
125	M	N	N	E	115.6	22.2	16.58	11.67	133.0	13.72	8.98	16.19	160.3	*
128	M	N	N	C2	114.7	15.9	12.08	12.21	134.6	15.29	10.86	17.71	167.7	*
131	M	Y	N	D	114.8	18.3	13.89	11.94	134.5	14.38	9.61	16.74	164.5	*
132	M	Y	N	E	116.3	20.0	14.76	9.98	126.7	12.78	10.36	*	*	*
133	F	N	N	A	113.1	18.8	14.67	9.66	120.9	13.19	9.58	15.85	154.3	14.00
134	M	N	N	C2	112.7	18.8	14.83	10.94	125.3	15.66	10.20	17.63	162.4	*
136	M	Y	Y	C1	117.4	19.8	14.39	12.59	142.2	15.00	10.03	17.68	172.7	*

ATOPY: 1 one or more atopic condition (I.e. asthma, hayfever, allergy, or eczema), 2 steriod treatment
MISSING DATA INDICATED BY *

SHORT CHILDREN

		ATOPY		SOCIAL	---PREPUBERTAL----			--TAKE-OFF--		PUBERTAL PEAK		-COMPLETION-		MENARCHE
ID	SEX	1	2	CLASS	HT(cm)	WT(kg)	BMI	AGE(y)	HT(cm)	AGE(y)	cm/y	AGE(Y)	HT(cm)	AGE(Y)
137	F	N	N	D	114.3	20.0	15.28	10.31	125.6	12.42	7.35	14.80	149.5	13.64
138	F	N	N	C2	113.7	17.9	13.86	7.03	107.8	9.80	8.61	11.87	137.7	10.53
139	F	N	N	B	114.2	17.7	13.59	10.84	126.4	12.85	6.29	14.83	145.4	14.50
140	F	N	N	D	112.6	18.5	14.58	11.97	130.3	14.41	8.10	15.98	152.7	15.42
142	M	Y	N	C2	112.7	20.6	16.22	12.39	135.2	14.14	8.63	16.47	160.5	*
144	F	N	N	E	113.1	17.9	13.95	*	*	*	*	*	*	13.94
145	M	N	N	A	113.9	20.3	15.68	11.06	129.6	13.58	10.80	16.13	165.4	*
146	M	N	N	C2	114.0	19.0	14.61	10.44	127.0	12.55	10.29	15.58	161.7	*
148	M	Y	Y	E	116.6	23.2	17.11	12.21	137.3	14.72	10.36	17.22	164.6	*
150	F	N	N	B	111.5	20.0	16.12	8.35	113.1	11.05	7.30	13.66	141.8	12.28
151	M	N	N	E	113.7	19.1	14.77	10.84	127.6	15.19	8.80	17.85	167.5	*
152	F	Y	Y	C2	114.5	18.3	13.92	9.78	125.8	11.64	7.72	14.18	151.4	13.31
154	F	N	N	D	114.8	24.3	18.42	8.44	116.9	11.43	9.81	13.45	148.2	12.06
155	M	Y	Y	C1	110.6	19.6	16.02	12.11	128.4	15.72	9.51	17.82	161.7	*
156	F	N	N	D	112.7	17.7	13.94	10.96	127.0	12.74	8.10	15.01	149.6	13.81
158	M	N	N	D	113.8	18.0	13.94	13.65	138.5	16.07	10.18	*	*	*
159	F	N	N	C2	115.6	21.4	15.97	10.11	126.6	13.41	8.85	15.80	158.6	14.72
161	M	Y	N	C2	116.3	18.5	13.71	10.26	126.4	13.92	8.09	16.32	160.6	*
163	M	Y	N	C2	114.5	19.9	15.17	13.14	139.8	15.28	9.07	17.58	163.6	*
164	M	Y	Y	C2	116.2	27.0	19.96	10.49	128.0	13.34	9.34	15.95	159.8	*
165	M	Y	Y	C1	115.2	18.8	14.19	10.21	125.5	12.93	12.71	15.39	162.7	*
169	M	N	N	D	114.0	18.8	14.48	11.53	134.1	14.47	8.50	17.17	167.4	*
172	M	N	N	C2	114.2	16.8	12.91	10.28	125.0	13.10	9.76	15.90	158.9	*
175	M	N	N	C2	110.0	16.6	13.75	12.63	130.7	14.99	10.63	16.63	158.2	*
177	M	Y	Y	B	110.0	20.8	17.15	11.09	127.3	14.30	7.08	16.24	155.1	*

ATOPY: 1 one or more atopic condition (I.e. asthma, hayfever, allergy, or eczema), 2 steriod treatment
MISSING DATA INDICATED BY *

CONTROL CHILDREN

		ATOPY		SOCIAL	---PREPUBERTAL----			--TAKE-OFF--		PUBERTAL PEAK		-COMPLETION-		MENARCHE
ID	SEX	1	2	CLASS	HT(cm)	WT(kg)	BMI	AGE(y)	HT(cm)	AGE(y)	cm/y	AGE(Y)	HT(cm)	AGE(Y)
202	M	N	N	A	128.0	27.8	16.97	10.43	143.0	12.96	10.10	14.93	174.7	*
204	F	Y	Y	D	127.2	23.2	14.34	11.10	142.5	12.92	8.27	14.63	163.0	14.33
205	M	N	N	C2	127.6	25.0	15.34	9.67	136.6	11.41	11.11	14.28	169.5	*
206	F	N	N	C2	129.4	23.6	14.10	10.58	142.1	12.00	7.17	14.03	159.1	14.27
207	F	N	N	B	124.6	23.4	15.06	9.35	131.3	11.42	7.20	13.83	156.6	12.84
208	F	Y	N	D	123.5	21.2	13.91	11.38	141.4	12.85	8.28	14.93	160.4	14.20
209	F	Y	N	D	128.0	34.5	21.10	12.98	151.4	14.16	5.07	15.47	162.2	14.65
210	F	N	N	C1	130.9	30.7	17.91	9.24	139.1	10.73	8.72	13.20	162.5	12.02
212	F	Y	Y	C2	119.9	-1.0	*	11.49	141.2	13.26	7.08	15.52	162.5	14.78
213	F	N	N	C2	124.5	21.8	14.04	10.54	138.9	12.08	7.43	14.45	161.9	13.56
214	F	Y	Y	C1	122.4	26.2	17.49	10.37	137.4	12.14	9.54	13.80	160.3	12.57
216	F	Y	Y	C2	124.1	23.4	15.18	12.17	143.2	14.17	7.73	16.16	166.6	15.39
219	F	Y	N	C1	129.5	30.3	18.07	8.82	133.8	11.44	8.65	13.85	163.2	12.46
220	M	N	N	B	124.9	24.2	15.51	10.88	139.2	13.33	10.25	15.42	169.5	*
221	F	N	N	C1	130.5	30.8	18.07	*	*	*	*	*	*	11.93
222	F	N	N	E	122.9	25.5	16.90	7.87	122.4	12.34	8.66	14.82	162.1	13.51
223	M	Y	Y	C1	135.7	31.1	16.88	9.45	144.3	12.44	13.93	15.00	184.4	*
224	F	Y	N	D	122.1	26.1	17.48	8.23	123.6	11.27	7.31	13.19	152.3	12.21
225	F	N	N	B	122.9	19.7	13.03	9.49	130.7	12.15	8.33	14.47	161.1	13.64
226	M	N	N	B	132.2	28.6	16.37	10.91	148.8	13.28	8.65	15.44	177.8	*
227	M	N	N	C2	127.1	22.6	13.97	11.62	147.0	15.10	10.41	16.76	180.0	*
228	F	Y	N	C1	125.3	24.0	15.26	8.56	128.7	11.75	8.17	13.48	161.5	13.05
229	F	Y	N	C2	127.4	23.1	14.21	10.64	142.7	11.79	6.17	14.13	159.0	12.99
231	M	Y	N	B	133.7	28.3	15.81	11.57	155.5	13.12	10.35	15.59	185.1	*
232	M	N	N	E	131.4	27.4	15.85	11.82	155.4	13.87	10.53	16.55	183.9	*
233	F	Y	N	B	124.1	22.1	14.35	9.01	127.3	12.65	7.07	14.99	157.3	13.60
234	M	Y	Y	C2	126.5	25.1	15.72	11.88	144.6	13.84	11.05	15.88	172.7	*

ATOPY: 1 one or more atopic condition (I.e. asthma, hayfever, allergy, or eczema), 2 steriod treatment
MISSING DATA INDICATED BY *

CONTROL CHILDREN

		ATOPY		SOCIAL	---PREPUBERTAL----			--TAKE-OFF--		PUBERTAL PEAK		-COMPLETION-		MENARCHE
ID	SEX	1	2	CLASS	HT(cm)	WT(kg)	BMI	AGE(y)	HT(cm)	AGE(y)	cm/y	AGE(Y)	HT(cm)	AGE(Y)
235	M	N	N	C2	127.0	23.5	14.54	11.55	142.4	13.38	10.02	16.07	173.3	*
236	F	N	N	C1	125.0	22.1	14.17	11.00	143.7	12.77	8.91	14.56	166.2	13.91
238	F	N	N	*	131.7	29.7	17.13	8.48	134.0	11.49	9.18	*	*	12.29
239	M	Y	Y	A	128.7	22.6	13.66	10.09	141.1	12.57	10.58	15.62	178.2	*
240	M	Y	Y	C2	128.0	26.3	16.04	12.64	153.2	14.57	10.44	16.78	181.9	*
241	F	N	N	C2	130.0	28.5	16.89	7.78	128.6	9.98	10.97	12.16	159.0	10.51
242	M	N	N	C2	124.9	24.9	15.93	9.64	135.2	12.61	11.01	15.01	174.4	*
246	M	N	N	C2	129.9	27.1	16.07	12.55	157.9	15.73	9.89	17.41	185.9	*
247	F	N	N	B	125.8	24.2	15.27	8.82	130.3	11.79	7.82	14.31	162.8	13.07
248	F	N	N	B	121.4	20.6	13.97	11.37	136.9	14.41	7.20	16.47	163.3	16.16
249	F	N	N	B	121.4	21.4	14.48	9.43	128.7	11.54	7.23	13.92	154.6	13.01
250	M	N	N	E	124.0	24.0	15.62	12.17	144.3	14.35	10.19	16.76	176.3	*
253	M	N	N	C2	131.9	31.8	18.29	9.28	139.8	12.17	9.94	14.82	175.3	*
254	F	N	N	D	125.9	26.5	16.71	9.13	131.6	12.47	8.51	14.05	159.5	12.81
255	F	Y	N	C2	122.7	21.2	14.08	9.74	133.9	12.47	7.92	14.72	163.7	13.92
259	F	N	N	C1	123.0	22.1	14.60	11.92	141.6	14.23	6.23	15.94	161.7	15.93
261	M	N	N	D	129.9	28.9	17.15	9.85	140.9	13.02	7.72	15.31	172.2	*
262	F	Y	N	C1	124.3	31.8	20.57	9.19	131.8	10.61	8.03	13.57	159.5	12.13
263	M	N	N	C2	126.3	22.8	14.29	14.98	157.9	16.61	8.14	18.21	173.8	*
266	M	Y	N	B	125.8	25.1	15.88	11.00	142.3	13.71	9.66	16.35	174.5	*
267	F	Y	Y	A	126.8	22.3	13.88	8.86	131.6	11.69	8.05	13.85	162.1	12.50
269	F	N	N	A	128.1	31.0	18.86	9.19	135.8	10.94	7.90	13.34	159.2	12.19
270	F	Y	N	E	122.5	24.8	16.51	11.49	141.8	13.03	7.77	15.06	161.4	14.03
271	M	N	N	B	125.9	23.4	14.74	13.02	152.8	15.00	9.31	17.14	179.0	*
272	M	N	N	B	129.4	24.0	14.33	11.17	147.4	13.70	9.92	15.65	178.1	*
273	F	N	N	C2	127.9	28.3	17.31	7.80	126.8	10.77	9.61	13.25	162.5	12.03
274	F	Y	N	C2	121.2	20.3	13.85	9.13	129.1	10.51	10.07	13.19	156.0	11.20

ATOPY: 1 one or more atopic condition (I.e. asthma, hayfever, allergy, or eczema), 2 steriod treatment
MISSING DATA INDICATED BY *

CONTROL CHILDREN

		ATOPY		SOCIAL	---PREPUBERTAL----			--TAKE-OFF--		PUBERTAL PEAK		-COMPLETION-		MENARCHE
ID	SEX	1	2	CLASS	HT(cm)	WT(kg)	BMI	AGE(y)	HT(cm)	AGE(y)	cm/y	AGE(Y)	HT(cm)	AGE(Y)
275	F	Y	Y	E	121.3	22.9	15.57	8.77	124.8	12.17	6.86	14.29	153.4	13.05
276	M	N	N	B	132.7	30.3	17.21	11.00	149.1	13.53	10.21	15.65	179.8	*
277	M	N	N	E	128.1	24.8	15.13	9.92	138.2	13.54	10.24	15.95	177.4	*
278	M	N	N	C2	127.5	25.0	15.40	13.13	153.4	16.46	9.22	18.26	182.4	*
279	M	N	N	D	120.2	19.8	13.68	10.90	135.8	14.82	10.90	17.44	174.4	*
280	M	N	N	B	120.4	22.1	15.24	9.06	125.6	13.50	9.91	15.63	164.5	*
281	F	Y	N	B	129.8	22.7	13.46	9.52	138.9	11.20	9.22	14.01	166.9	13.36
282	F	Y	N	B	128.1	23.2	14.13	11.09	147.4	12.96	8.73	15.09	173.0	14.20
283	F	N	N	C2	120.7	22.1	15.19	10.80	136.1	12.57	7.55	14.33	154.9	13.59
285	M	Y	N	D	127.7	24.9	15.28	13.28	151.0	16.18	9.98	18.42	177.5	*
287	F	N	N	C1	122.4	21.0	14.02	9.66	130.7	12.31	8.34	14.19	156.8	12.86
288	M	Y	N	D	129.6	24.5	14.57	10.01	141.7	12.91	8.72	15.53	177.1	*
290	M	N	N	C2	125.4	24.4	15.51	13.26	153.1	15.30	8.83	*	*	*
291	M	N	N	E	129.5	34.8	20.75	11.74	148.2	15.12	9.53	16.81	176.7	*
292	M	N	N	E	127.8	26.3	16.12	11.09	145.0	13.68	9.42	16.06	178.3	*
294	M	N	N	C1	121.1	-1.0	*	10.99	141.6	14.09	9.67	16.25	173.6	*
295	F	N	N	C1	128.0	24.0	14.64	10.28	140.9	12.47	5.33	15.14	164.0	14.14
296	M	Y	N	C2	123.8	26.0	16.99	9.78	133.4	12.62	10.44	15.15	171.8	*
301	M	Y	Y	C1	124.8	22.5	14.46	12.78	148.3	14.48	9.81	16.47	171.8	*
302	M	N	N	C1	129.6	25.4	15.11	9.99	139.0	13.56	10.22	15.63	174.0	*
303	M	N	N	A	131.3	25.8	14.98	8.53	134.5	12.09	11.52	15.05	181.9	*
305	F	N	N	E	128.5	30.0	18.16	9.05	133.7	11.18	8.23	13.04	157.3	11.81
308	M	N	N	B	128.2	24.2	14.70	11.39	147.7	13.88	10.79	16.45	181.6	*
309	F	N	N	E	128.2	26.1	15.89	*	*	*	*	*	*	13.52
310	M	N	N	A	125.9	24.0	15.14	10.55	140.4	13.18	11.60	15.11	174.3	*
312	F	Y	N	D	123.4	23.7	15.54	7.89	122.9	11.48	7.73	13.87	157.8	12.77
313	F	N	N	D	120.6	21.5	14.81	9.97	132.7	11.79	8.96	13.45	154.2	12.30

ATOPY: 1 one or more atopic condition (I.e. asthma, hayfever, allergy, or eczema), 2 steriod treatment
MISSING DATA INDICATED BY *

CONTROL CHILDREN

ID	SEX	ATOPY 1	ATOPY 2	SOCIAL CLASS	---PREPUBERTAL---- HT(cm)	WT(kg)	BMI	--TAKE-OFF-- AGE(y)	HT(cm)	PUBERTAL PEAK AGE(y)	cm/y	-COMPLETION- AGE(Y)	HT(cm)	MENARCHE AGE(Y)
314	M	N	N	B	122.9	24.3	16.06	11.32	140.5	13.86	10.32	16.22	173.0	*
316	M	N	Y	C2	128.7	22.3	13.47	10.01	141.7	11.83	10.27	14.74	177.1	*
319	M	N	N	C2	123.0	21.3	14.10	11.19	137.3	*	*	16.08	167.9	*
321	F	N	N	C1	124.7	26.3	16.91	8.19	125.6	12.09	8.80	14.13	161.9	12.72
322	F	Y	Y	C2	121.7	23.8	16.04	10.00	131.7	12.00	8.44	13.93	154.0	12.62
323	M	N	N	E	130.2	27.3	16.13	10.81	144.3	14.14	9.30	16.23	179.9	*
324	M	N	N	D	119.0	20.7	14.60	11.13	136.9	13.49	11.01	16.20	170.7	*
328	M	N	N	B	132.2	26.0	14.90	10.69	149.2	12.69	10.78	15.68	180.5	*
330	F	N	N	C1	129.2	34.7	20.81	10.56	145.0	11.89	7.36	13.57	162.8	12.58
332	M	Y	Y	E	122.3	23.7	15.87	13.48	147.8	16.11	7.65	18.00	171.6	*
333	F	N	N	C2	125.9	22.3	14.09	8.58	129.2	10.67	9.52	13.10	158.5	12.44
334	M	Y	Y	B	130.4	29.1	17.12	10.84	146.0	13.33	8.84	15.59	174.6	*
336	M	N	N	E	125.3	25.1	15.96	11.84	147.5	13.78	9.91	15.44	171.8	*
338	F	N	N	C2	128.4	29.0	17.62	8.99	133.8	10.93	9.20	13.55	159.9	11.73
340	F	Y	Y	C2	127.6	28.5	17.50	10.44	142.4	13.15	7.32	14.85	165.8	14.50
343	M	N	N	B	129.3	27.2	16.30	11.59	150.9	13.21	10.98	15.89	178.3	*
346	M	Y	Y	C1	123.7	23.6	15.41	12.44	145.3	15.54	8.50	17.52	174.6	*
347	M	N	N	D	131.7	25.9	14.92	8.84	135.7	12.52	11.98	15.49	183.1	*
348	M	Y	Y	C1	133.5	27.3	15.34	11.32	150.9	15.96	8.22	18.55	190.6	*
350	F	N	N	B	125.3	24.9	15.89	8.33	127.0	10.92	8.80	13.91	161.5	12.56
351	M	N	N	C2	135.4	29.7	16.18	11.22	153.6	12.93	8.85	16.15	185.3	*
352	F	N	N	E	121.3	23.5	15.94	9.70	130.3	13.39	7.70	15.28	161.6	12.90
354	F	Y	Y	D	123.2	25.3	16.71	10.45	135.4	11.75	6.80	13.85	151.2	12.61
355	M	N	N	C2	132.9	41.5	23.47	11.31	152.6	13.34	11.27	15.63	180.7	*
356	F	N	N	E	133.6	35.3	19.79	11.61	159.6	12.27	8.64	13.67	173.1	12.93
358	M	N	N	E	123.6	23.6	15.45	9.21	129.5	12.89	11.56	14.86	167.2	*
359	F	Y	N	E	127.2	30.0	18.56	8.80	131.7	11.02	6.70	13.31	157.3	12.32

ATOPY: 1 one or more atopic condition (I.e. asthma, hayfever, allergy, or eczema), 2 steriod treatment
MISSING DATA INDICATED BY *

CONTROL CHILDREN

		ATOPY		SOCIAL	---PREPUBERTAL----			--TAKE-OFF--		PUBERTAL PEAK		-COMPLETION-		MENARCHE
ID	SEX	1	2	CLASS	HT(cm)	WT(kg)	BMI	AGE(y)	HT(cm)	AGE(y)	cm/y	AGE(Y)	HT(cm)	AGE(Y)
360	M	N	N	C1	124.6	23.7	15.25	13.96	153.4	16.45	6.91	17.86	172.7	*
363	M	Y	N	C1	125.4	24.8	15.77	13.66	153.3	16.18	6.63	18.50	177.1	*
364	M	N	Y	C2	125.0	22.6	14.49	8.99	130.7	12.06	11.88	15.41	174.3	*
365	M	Y	Y	C2	127.3	24.0	14.81	11.09	143.8	13.63	9.72	15.64	174.8	*
368	F	N	N	C2	127.5	24.8	15.24	8.45	129.7	12.13	7.66	14.81	166.5	13.91
370	M	N	N	C2	132.2	29.1	16.62	11.68	151.2	14.14	10.97	16.46	184.0	*
371	M	N	N	D	131.4	22.9	13.28	10.60	145.2	12.62	10.70	15.63	178.6	*
372	M	N	N	C1	129.8	29.9	17.78	10.56	143.1	13.19	9.09	16.24	176.9	*
373	M	Y	N	C2	128.5	28.2	17.10	9.49	136.0	13.44	10.59	16.18	175.4	*
375	M	Y	Y	C2	132.2	30.1	17.23	10.89	149.1	13.25	11.99	16.06	186.5	*
376	M	N	N	C2	128.2	27.1	16.49	10.18	141.4	12.99	11.86	15.15	176.2	*

ATOPY: 1 one or more atopic condition (I.e. asthma, hayfever, allergy, or eczema), 2 steriod treatment
MISSING DATA INDICATED BY *

APPENDIX C

Final height data for Chapter 5

SHORT CHILDREN

		AT AGE 6 YRS		-FINAL MEASUREMENT--			-PREDICTED--		---TARGET---	
ID	SEX	HT(cm)	HSDS	AGE(y)	HT(cm)	HSDS	HT(cm)	HSDS	HT(cm)	HSDS
1	F	102.6	-2.63	19.90	151.1	-2.08	155.0	-1.47	155.8	-1.34
3	F	103.9	-2.36	18.08	151.9	-1.93	155.9	-1.31	152.8	-1.83
4	F	103.1	-2.52	18.00	149.9	-2.26	153.3	-1.75	152.8	-1.83
5	M	103.4	-2.59	19.20	165.2	-1.73	161.2	-2.50	170.9	-1.08
6	F	103.9	-2.35	19.10	154.2	-1.56	157.6	-1.03	156.2	-1.27
7	F	103.3	-2.48	18.03	154.7	-1.47	*	*	150.9	-2.14
8	F	102.0	-2.75	16.13	152.2	-1.82	*	*	158.7	-.84
9	F	104.0	-2.34	18.09	148.0	-2.58	153.7	-1.68	152.9	-1.81
10	F	102.5	-2.64	15.64	148.2	-2.41	155.4	-1.40	154.9	-1.48
11	M	101.1	-3.06	16.31	161.3	-1.75	158.2	-2.93	163.4	-2.17
14	F	103.4	-2.45	18.91	153.3	-1.71	153.7	-1.67	156.6	-1.20
16	F	101.2	-2.91	18.36	142.5	-3.49	153.9	-1.65	156.3	-1.25
18	F	104.8	-2.18	16.41	158.3	-.84	156.8	-1.17	154.9	-1.48
19	F	104.1	-2.32	18.18	151.7	-1.97	155.6	-1.36	156.2	-1.27
20	M	104.1	-2.43	19.38	164.5	-1.83	161.6	-2.44	168.3	-1.45
21	F	104.0	-2.34	18.30	150.7	-2.14	156.8	-1.16	152.7	-1.85
22	F	103.6	-2.42	18.95	149.7	-2.31	155.3	-1.42	156.6	-1.19
23	M	104.1	-2.43	19.46	170.1	-1.03	163.1	-2.22	175.6	-.38
24	F	104.4	-2.25	13.73	146.2	-1.87	154.8	-1.50	155.6	-1.36
26	M	102.4	-2.78	19.68	163.5	-1.98	*	*	163.2	-2.20
27	M	104.5	-2.36	19.61	166.1	-1.61	163.4	-2.18	174.0	-.62
28	F	99.9	-3.17	19.55	147.7	-2.64	152.5	-1.87	153.2	-1.76
29	F	103.8	-2.37	19.06	156.9	-1.11	154.2	-1.60	152.3	-1.91
30	F	102.2	-2.71	18.57	153.5	-1.67	157.9	-.98	150.4	-2.22
32	M	103.4	-2.59	20.08	169.3	-1.16	160.7	-2.57	164.7	-1.98
33	F	101.8	-2.79	18.17	150.2	-2.22	153.2	-1.77	159.9	-.64
34	M	104.6	-2.33	18.53	162.1	-2.17	*	*	160.9	-2.54

MISSING DATA INDICATED BY *

SHORT CHILDREN

		AT AGE 6 YRS		-FINAL MEASUREMENT--			-PREDICTED--		---TARGET---	
ID	SEX	HT(cm)	HSDS	AGE(y)	HT(cm)	HSDS	HT(cm)	HSDS	HT(cm)	HSDS
36	F	102.4	-2.67	18.72	147.2	-2.72	152.9	-1.82	147.7	-2.68
38	F	103.9	-2.36	18.87	153.6	-1.66	157.3	-1.08	164.2	.06
39	M	100.1	-3.26	17.55	164.5	-1.73	157.4	-3.05	165.9	-1.81
40	M	101.7	-2.93	18.56	156.3	-3.00	159.7	-2.72	169.9	-1.21
41	F	101.2	-2.90	20.17	151.6	-2.00	154.1	-1.61	158.7	-.86
42	M	104.3	-2.39	19.47	169.1	-1.18	162.9	-2.25	164.0	-2.09
47	F	100.0	-3.16	18.03	142.5	-3.49	153.1	-1.77	149.7	-2.34
48	F	100.3	-3.11	19.19	144.7	-3.13	151.7	-2.01	161.4	-.40
49	F	103.1	-2.51	19.22	152.5	-1.84	153.8	-1.67	159.8	-.66
50	M	102.3	-2.80	18.08	170.7	-.92	160.3	-2.63	174.4	-.56
51	M	104.3	-2.40	19.09	155.4	-3.14	162.4	-2.32	160.7	-2.56
53	M	102.9	-2.69	19.45	167.1	-1.46	160.7	-2.56	172.0	-.92
54	F	102.6	-2.62	19.17	150.3	-2.21	*	*	156.0	-1.30
59	F	103.8	-2.37	19.25	156.3	-1.21	*	*	159.4	-.73
61	M	103.7	-2.51	18.79	166.9	-1.49	162.2	-2.35	167.5	-1.57
63	M	105.2	-2.21	19.79	163.9	-1.92	163.4	-2.17	173.2	-.74
64	M	102.4	-2.79	19.45	161.2	-2.31	160.6	-2.58	167.5	-1.57
67	F	102.9	-2.56	18.75	147.1	-2.74	156.2	-1.27	159.0	-.80
70	F	98.7	-3.43	19.30	146.7	-2.80	152.3	-1.92	158.7	-.86
71	M	101.8	-2.92	18.20	168.1	-1.30	159.5	-2.75	168.5	-1.43
72	M	104.1	-2.44	20.17	169.2	-1.17	*	*	168.7	-1.39
73	F	102.7	-2.60	18.70	146.6	-2.82	155.1	-1.44	155.7	-1.34
74	F	102.7	-2.61	18.35	153.4	-1.69	155.1	-1.44	152.4	-1.90
76	M	103.4	-2.57	20.15	169.4	-1.14	162.0	-2.37	171.6	-.98
77	M	103.3	-2.60	19.01	174.8	-.36	162.3	-2.33	170.4	-1.15
79	M	102.9	-2.68	20.33	158.0	-2.79	157.0	-3.11	169.1	-1.33
85	M	104.5	-2.36	19.72	159.8	-2.51	162.9	-2.25	165.0	-1.94

MISSING DATA INDICATED BY *

SHORT CHILDREN

		AT AGE 6 YRS		-FINAL MEASUREMENT--			-PREDICTED--		---TARGET---	
ID	SEX	HT(cm)	HSDS	AGE(y)	HT(cm)	HSDS	HT(cm)	HSDS	HT(cm)	HSDS
87	F	103.5	-2.44	18.72	145.4	-3.02	153.0	-1.79	149.4	-2.40
89	M	101.1	-3.06	19.96	158.8	-2.66	*	*	160.4	-2.61
90	M	101.4	-3.00	19.90	159.6	-2.54	*	*	160.4	-2.61
94	M	103.8	-2.49	19.29	163.1	-2.03	161.9	-2.39	160.3	-2.62
95	F	100.2	-3.12	19.91	153.3	-1.71	152.6	-1.86	157.3	-1.09
96	M	105.1	-2.23	20.19	166.7	-1.53	163.7	-2.13	*	*
101	M	100.8	-3.11	19.13	168.0	-1.33	160.2	-2.63	168.8	-1.39
102	M	101.7	-2.93	19.11	160.8	-2.36	158.6	-2.87	165.5	-1.86
103	M	98.0	-3.68	19.66	161.8	-2.22	154.1	-3.53	169.6	-1.26
105	F	101.8	-2.78	18.97	149.8	-2.29	154.9	-1.48	160.5	-.55
108	M	104.0	-2.46	18.54	161.0	-2.33	161.5	-2.45	171.9	-.93
110	M	105.5	-2.14	19.10	162.2	-2.16	*	*	174.4	-.56
113	F	100.8	-2.99	19.46	151.2	-2.06	*	*	148.0	-2.62
114	M	103.6	-2.54	18.53	159.6	-2.53	162.2	-2.35	164.5	-2.01
116	M	102.9	-2.68	20.44	165.2	-1.76	*	*	165.0	-1.93
118	M	96.3	-4.04	20.27	163.4	-2.01	151.4	-3.92	166.8	-1.67
119	M	105.3	-2.20	18.80	166.2	-1.59	*	*	169.0	-1.35
121	F	101.9	-2.77	18.02	150.3	-2.20	153.9	-1.64	153.5	-1.71
125	M	104.3	-2.39	18.89	161.0	-2.33	*	*	167.5	-1.58
128	M	104.2	-2.42	19.15	169.4	-1.13	162.9	-2.25	171.7	-.96
131	M	103.0	-2.67	19.04	165.2	-1.73	160.9	-2.54	171.1	-1.05
133	F	102.2	-2.71	18.24	155.6	-1.32	155.0	-1.46	164.1	.05
134	M	102.5	-2.77	19.98	163.7	-1.96	159.9	-2.68	163.2	-2.20
136	M	105.2	-2.21	19.12	174.4	-.41	164.3	-2.04	175.5	-.40
137	F	102.8	-2.59	18.63	152.1	-1.91	154.5	-1.55	153.4	-1.73
138	F	102.2	-2.71	17.55	140.6	-3.79	*	*	155.7	-1.34
139	F	102.4	-2.66	19.16	148.8	-2.46	154.1	-1.62	154.9	-1.48

MISSING DATA INDICATED BY *

SHORT CHILDREN

		AT AGE 6 YRS		-FINAL MEASUREMENT--			-PREDICTED--		---TARGET---	
ID	SEX	HT(cm)	HSDS	AGE(y)	HT(cm)	HSDS	HT(cm)	HSDS	HT(cm)	HSDS
140	F	102.0	-2.75	17.57	154.1	-1.56	*	*	154.4	-1.55
142	M	102.4	-2.79	18.96	161.7	-2.23	159.9	-2.68	169.8	-1.24
144	F	103.0	-2.54	15.95	150.8	-2.03	153.7	-1.68	*	*
145	M	102.2	-2.82	18.86	167.9	-1.34	160.3	-2.62	165.7	-1.84
146	M	102.0	-2.87	18.98	162.5	-2.12	159.8	-2.70	164.4	-2.02
148	M	104.7	-2.31	19.22	167.7	-1.37	163.4	-2.17	169.3	-1.30
150	F	100.7	-3.02	16.85	144.0	-3.22	151.6	-2.02	153.1	-1.78
151	M	104.0	-2.45	19.09	169.8	-1.07	*	*	166.4	-1.73
152	F	103.3	-2.47	19.36	153.1	-1.74	*	*	155.4	-1.39
154	F	102.9	-2.57	18.26	152.3	-1.87	156.1	-1.29	155.7	-1.34
155	M	102.6	-2.74	19.22	162.8	-2.08	162.1	-2.35	170.9	-1.07
156	F	103.2	-2.49	17.45	151.4	-2.00	*	*	147.2	-2.76
158	M	103.2	-2.63	20.86	171.5	-.87	162.1	-2.37	172.4	-.85
159	F	103.3	-2.47	18.53	158.7	-.81	154.5	-1.54	165.6	.29
161	M	104.3	-2.38	18.09	162.5	-2.09	162.4	-2.32	*	*
163	M	104.0	-2.45	18.82	166.2	-1.59	162.8	-2.25	172.0	-.91
164	M	103.8	-2.51	18.52	162.2	-2.16	161.6	-2.44	162.1	-2.36
165	M	104.1	-2.43	18.67	165.1	-1.74	162.7	-2.27	171.5	-.98
169	M	103.9	-2.47	19.41	169.9	-1.06	162.6	-2.29	173.8	-.66
172	M	103.4	-2.58	18.35	160.8	-2.35	161.2	-2.49	166.6	-1.70
175	M	100.9	-3.10	19.59	161.3	-2.29	158.0	-2.96	167.4	-1.58
177	M	99.9	-3.30	19.31	157.5	-2.84	157.3	-3.07	161.7	-2.41

MISSING DATA INDICATED BY *

CONTROL CHILDREN

		AT AGE 6 YRS		-FINAL MEASUREMENT--			-PREDICTED--		---TARGET---	
ID	SEX	HT(cm)	HSDS	AGE(y)	HT(cm)	HSDS	HT(cm)	HSDS	HT(cm)	HSDS
202	M	115.7	-.04	19.23	177.1	-.03	*	*	179.1	.13
205	M	*	*	19.67	173.1	-.60	*	*	171.6	-.98
206	F	117.3	.40	18.72	162.1	-.25	*	*	163.2	-.11
207	F	112.4	-.60	18.42	159.0	-.76	*	*	160.9	-.48
208	F	111.2	-.85	19.05	162.5	-.19	*	*	160.4	-.57
209	F	115.9	.12	18.22	163.8	.03	*	*	156.4	-1.23
210	F	117.8	.50	19.09	165.5	.31	*	*	164.1	.05
212	F	*	*	19.09	164.4	.13	*	*	160.5	-.56
213	F	112.6	-.56	17.88	163.6	.01	*	*	161.3	-.42
214	F	110.1	-1.08	18.92	163.0	-.10	*	*	160.5	-.55
216	F	112.8	-.53	19.29	168.7	.84	*	*	173.4	1.59
219	F	117.0	.33	18.87	165.1	.24	*	*	168.8	.82
220	M	112.0	-.81	19.54	173.1	-.60	*	*	170.4	-1.14
221	F	117.4	.44	18.69	168.6	.82	*	*	167.6	.63
222	F	113.2	-.43	18.24	163.9	.05	*	*	160.5	-.56
223	M	122.3	1.32	19.30	186.1	1.26	*	*	184.0	.85
224	F	110.4	-1.01	18.05	155.4	-1.35	*	*	157.6	-1.04
225	F	111.8	-.74	18.98	162.1	-.25	*	*	161.7	-.35
226	M	119.9	.81	19.69	180.0	.39	*	*	181.3	.45
227	M	115.6	-.08	19.89	180.9	.51	*	*	178.7	.07
228	F	112.4	-.60	18.22	163.6	.00	*	*	154.8	-1.50
231	M	120.7	.97	19.57	186.2	1.28	*	*	178.2	.00
232	M	118.1	.44	19.78	184.4	1.02	*	*	*	*
233	F	113.1	-.45	18.77	160.6	-.50	*	*	160.5	-.56
234	M	115.4	-.10	19.49	175.5	-.26	*	*	173.5	-.70
235	M	116.4	.10	19.63	175.2	-.30	*	*	*	*
236	F	113.3	-.43	18.65	168.2	.76	*	*	160.4	-.56

MISSING DATA INDICATED BY *

CONTROL CHILDREN

		AT AGE 6 YRS		-FINAL MEASUREMENT--			-PREDICTED--		---TARGET---	
ID	SEX	HT(cm)	HSDS	AGE(y)	HT(cm)	HSDS	HT(cm)	HSDS	HT(cm)	HSDS
239	M	116.3	.08	20.12	180.1	.39	*	*	183.4	.76
240	M	115.5	-.09	19.56	183.2	.85	*	*	178.0	-.04
241	F	116.9	.32	19.17	162.9	-.12	*	*	166.1	.37
242	M	111.2	-.98	19.56	175.5	-.26	*	*	169.4	-1.29
246	M	116.9	.20	20.54	186.3	1.27	*	*	182.8	.66
247	F	114.1	-.25	18.42	165.2	.26	*	*	161.2	-.43
248	F	109.9	-1.13	19.88	166.1	.41	*	*	161.0	-.47
249	F	110.4	-1.02	19.03	158.3	-.88	*	*	160.9	-.48
250	M	112.0	-.81	18.47	177.9	.09	*	*	180.2	.28
253	M	118.0	.42	19.10	174.7	-.37	*	*	171.0	-1.05
254	F	113.8	-.32	19.12	161.3	-.39	*	*	169.1	.87
255	F	112.1	-.67	19.15	165.6	.33	*	*	162.5	-.22
259	F	112.5	-.58	19.18	163.7	.01	*	*	155.1	-1.44
261	M	116.3	.08	18.89	174.5	-.40	*	*	173.4	-.71
262	F	112.6	-.57	18.33	165.3	.28	*	*	*	*
263	M	113.8	-.44	19.76	176.4	-.13	*	*	175.2	-.45
266	M	*	*	20.30	176.0	-.20	*	*	174.0	-.63
267	F	115.6	.05	18.30	165.3	.28	*	*	167.6	.62
269	F	*	*	19.43	160.2	-.57	*	*	162.7	-.18
270	F	109.7	-1.15	18.34	163.2	-.07	*	*	162.6	-.20
271	M	113.3	-.55	20.24	183.0	.81	*	*	179.6	.20
272	M	117.6	.35	19.54	181.4	.59	*	*	174.7	-.51
273	F	114.9	-.10	18.88	164.9	.21	*	*	168.8	.82
274	F	109.3	-1.25	18.96	158.5	-.85	*	*	161.3	-.42
275	F	110.4	-1.02	17.93	156.3	-1.20	*	*	164.0	.02
276	M	121.0	1.05	19.31	181.1	.55	*	*	176.7	-.22
277	M	115.6	-.07	19.82	180.0	.38	*	*	175.5	-.41

MISSING DATA INDICATED BY *

CONTROL CHILDREN

		AT AGE 6 YRS		-FINAL MEASUREMENT--			-PREDICTED--		---TARGET---	
ID	SEX	HT(cm)	HSDS	AGE(y)	HT(cm)	HSDS	HT(cm)	HSDS	HT(cm)	HSDS
278	M	115.6	-.07	19.75	185.9	1.23	*	*	187.0	1.28
279	M	108.9	-1.45	19.81	173.8	-.50	*	*	177.4	-.13
280	M	110.5	-1.12	18.88	165.9	-1.63	*	*	174.8	-.51
281	F	115.8	.10	18.55	168.1	.74	*	*	166.4	.44
282	F	113.7	-.34	18.49	175.2	1.92	*	*	166.1	.37
283	F	110.1	-1.08	18.91	159.7	-.65	*	*	164.4	.10
285	M	116.4	.10	19.86	178.6	.18	*	*	181.4	.47
287	F	110.9	-.91	20.12	157.5	-1.02	*	*	160.5	-.56
288	M	118.4	.52	18.95	179.3	.29	*	*	174.6	-.53
291	M	117.1	.24	20.01	180.3	.42	*	*	178.9	.10
292	M	114.1	-.38	18.78	179.5	.32	*	*	179.7	.21
294	M	*	*	18.83	176.7	-.08	*	*	179.7	.21
295	F	114.6	-.14	19.03	165.5	.31	*	*	164.8	.16
296	M	111.7	-.86	16.64	175.6	.06	*	*	168.1	-1.48
301	M	113.2	-.56	19.34	174.3	-.43	*	*	175.2	-.44
302	M	116.9	.20	18.39	174.9	-.33	*	*	175.0	-.47
303	M	120.4	.92	19.02	184.0	.96	*	*	180.0	.25
305	F	116.8	.30	19.44	157.8	-.97	*	*	155.4	-1.40
308	M	116.0	.00	19.16	183.7	.92	*	*	178.5	.03
309	F	114.5	-.18	16.52	169.4	.99	*	*	161.7	-.35
310	M	115.0	-.18	17.89	175.6	-.20	*	*	177.4	-.12
312	F	111.2	-.86	17.47	161.5	-.34	*	*	161.3	-.42
313	F	110.6	-.98	18.23	155.3	-1.37	*	*	152.6	-1.87
314	M	111.2	-.97	18.53	174.6	-.38	*	*	179.9	.24
316	M	115.4	-.11	18.70	181.6	.62	*	*	175.4	-.41
319	M	112.0	-.82	18.27	168.8	-1.20	*	*	172.1	-.90
321	F	112.3	-.63	19.15	164.5	.14	*	*	157.5	-1.05

MISSING DATA INDICATED BY *

CONTROL CHILDREN

		AT AGE 6 YRS		-FINAL MEASUREMENT--			-PREDICTED--		---TARGET---	
ID	SEX	HT(cm)	HSDS	AGE(y)	HT(cm)	HSDS	HT(cm)	HSDS	HT(cm)	HSDS
322	F	109.5	-1.20	18.92	155.9	-1.28	*	*	161.7	-.35
323	M	118.2	.48	18.63	183.7	.92	*	*	183.5	.77
324	M	108.1	-1.62	19.33	172.7	-.66	*	*	174.5	-.55
328	M	117.6	.35	18.49	180.3	.44	*	*	181.1	.42
330	F	115.8	.09	17.81	164.8	.21	*	*	164.6	.13
332	M	111.8	-.85	19.42	172.0	-.76	*	*	179.9	.24
333	F	114.1	-.26	18.16	161.0	-.43	*	*	160.2	-.60
334	M	116.6	.14	17.04	176.7	.10	*	*	177.7	-.08
338	F	116.9	.32	19.65	162.2	-.24	*	*	*	*
340	F	115.4	.01	18.94	165.3	.28	*	*	167.8	.66
343	M	*	*	17.68	179.2	.33	*	*	*	*
346	M	111.5	-.91	18.66	178.1	.12	*	*	177.4	-.12
347	M	119.3	.69	18.23	184.5	1.05	*	*	177.0	-.18
348	M	120.0	.84	19.82	191.4	2.02	*	*	177.9	-.06
350	F	*	*	17.99	162.2	-.23	*	*	160.2	-.60
351	M	121.3	1.11	18.59	186.7	1.35	*	*	177.6	-.10
352	F	110.4	-1.01	18.07	162.2	-.23	*	*	163.0	-.13
354	F	110.7	-.96	18.04	153.3	-1.70	*	*	*	*
355	M	119.7	.78	18.97	182.1	.69	*	*	183.2	.73
356	F	118.2	.59	19.24	175.7	2.00	*	*	170.5	1.10
358	M	112.9	-.61	19.24	170.6	-.96	*	*	172.7	-.81
359	F	114.3	-.21	18.40	159.7	-.65	*	*	160.8	-.51
360	M	111.6	-.89	20.23	175.0	-.34	*	*	175.9	-.35
363	M	113.2	-.56	20.33	178.3	.13	*	*	178.6	.05
364	M	113.2	-.55	16.08	175.5	.25	*	*	177.8	-.06
365	M	115.7	-.04	18.38	178.7	.21	*	*	177.8	-.06
368	F	115.0	-.06	17.92	166.9	.55	*	*	162.4	-.23

MISSING DATA INDICATED BY *

CONTROL CHILDREN

		AT AGE 6 YRS		-FINAL MEASUREMENT--			-PREDICTED--		---TARGET---	
ID	SEX	HT(cm)	HSDS	AGE(y)	HT(cm)	HSDS	HT(cm)	HSDS	HT(cm)	HSDS
370	M	120.0	.84	18.96	186.2	1.28	*	*	179.0	.12
371	M	119.9	.82	18.39	179.2	.28	*	*	172.5	-.84
372	M	116.9	.20	19.34	179.4	.30	*	*	183.5	.76
373	M	117.0	.21	19.07	174.4	-.41	*	*	176.8	-.21
375	M	119.4	.72	18.51	186.4	1.31	*	*	*	*
376	M	115.6	-.06	18.97	179.6	.33	*	*	175.2	-.45

MISSING DATA INDICATED BY *

APPENDIX D

The Preece-Baines Biological Parameters for Chapter 7

SHORT CHILDREN

		-------TAKE-OFF--------			-----PUBERTAL PEAK------			FINAL HEIGHT
ID	**SEX**	**AGE(y)**	**HT(cm)**	**VEL(cm/y)**	**AGE(y)**	**HT (cm)**	**VEL(cm/y)**	**(cm)**
1	F	8.74	115.73	4.56	12.40	136.38	7.21	152.13
3	F	9.38	119.75	4.14	12.76	138.52	7.76	152.09
4	F	10.81	121.84	3.18	14.24	138.17	7.52	149.66
5	M	10.29	125.02	4.44	13.80	148.18	10.27	164.51
6	F	9.67	123.63	4.63	12.65	140.76	7.35	153.80
7	F	8.00	114.81	5.47	11.40	136.95	7.96	154.59
8	F	8.11	114.23	5.36	11.44	135.38	7.72	152.34
9	F	8.63	117.47	4.67	11.51	135.18	8.42	148.11
10	F	9.24	118.96	4.36	11.99	135.77	8.96	147.75
11	M	9.62	121.11	5.01	13.02	144.93	10.21	161.91
14	F	8.70	118.35	5.19	11.91	137.48	6.99	153.62
16	F	8.92	115.86	4.49	11.48	131.34	8.46	142.53
18	F	9.86	128.75	5.25	12.53	145.38	7.60	158.68
19	F	7.83	112.72	4.66	11.59	135.87	8.48	152.72
20	M	10.54	126.98	4.35	14.45	148.46	7.19	164.55
21	F	9.36	122.40	4.69	12.11	138.52	7.56	150.71
22	F	7.76	113.38	5.31	10.97	133.26	7.39	149.60
23	M	11.53	133.01	4.20	14.94	155.06	10.45	170.55
24	F	8.00	114.70	4.91	10.97	132.98	8.01	146.74
26	M	11.23	127.29	4.12	15.15	148.56	7.45	164.07
27	M	11.57	130.39	3.89	15.56	151.53	7.51	166.74
28	F	9.07	114.43	4.28	12.41	132.82	7.35	146.43
29	F	10.23	126.09	4.42	13.22	144.46	8.92	157.59
30	F	8.46	115.48	4.98	11.86	136.84	8.19	152.88
32	M	12.60	134.88	3.68	16.28	155.07	8.59	169.29
33	F	10.01	119.88	3.85	13.35	137.92	7.92	150.78
34	M	10.34	126.08	4.28	13.89	146.89	8.40	161.81

SHORT CHILDREN

		-------TAKE-OFF--------			-----PUBERTAL PEAK------			FINAL HEIGHT
ID	**SEX**	**AGE(y)**	**HT(cm)**	**VEL(cm/y)**	**AGE(y)**	**HT (cm)**	**VEL(cm/y)**	**(cm)**
36	F	10.10	123.05	4.09	12.79	136.96	6.78	147.37
38	F	8.84	119.44	5.09	12.00	139.85	8.52	155.07
39	M	9.56	118.99	4.85	13.60	145.90	9.53	165.20
40	M	10.04	119.33	3.88	13.70	141.15	9.61	156.49
41	F	8.38	113.67	4.97	11.82	135.08	8.05	151.24
42	M	10.86	133.60	5.14	14.21	153.96	7.37	170.35
47	F	8.87	115.08	4.61	11.51	130.73	7.91	142.30
48	F	9.12	114.48	4.13	12.34	132.05	7.47	144.86
49	F	10.38	124.82	4.11	13.41	140.02	6.32	151.75
50	M	10.76	128.86	4.62	14.10	153.03	11.91	170.02
51	M	10.11	124.45	4.12	13.05	143.03	10.15	156.09
53	M	10.88	124.80	3.91	15.10	149.43	9.16	166.79
54	F	10.44	124.19	3.86	13.25	139.61	8.20	150.56
59	F	9.72	123.24	4.64	12.97	142.35	7.67	156.66
61	M	9.98	123.62	4.51	14.07	149.11	8.96	167.36
63	M	10.74	129.44	4.29	14.16	149.64	8.52	164.09
64	M	9.93	122.78	4.59	13.66	144.86	7.91	161.17
67	F	8.89	115.82	4.09	12.32	134.16	7.25	147.60
70	F	10.36	120.54	4.03	13.05	135.48	7.96	146.18
71	M	11.27	130.70	4.49	14.78	152.25	8.76	167.73
72	M	11.18	132.07	4.49	14.65	154.01	9.27	169.63
73	F	8.44	114.56	4.49	11.54	133.47	8.65	147.08
74	F	9.46	119.37	4.40	12.84	139.27	8.17	153.69
76	M	12.47	133.55	3.57	15.79	154.32	11.48	169.00
77	M	11.28	140.35	5.51	14.17	159.94	8.61	174.97
79	M	12.35	130.91	3.36	15.74	146.77	6.78	158.10
85	M	11.58	132.72	3.76	14.43	147.71	7.70	158.40

SHORT CHILDREN

		-------TAKE-OFF--------			-----PUBERTAL PEAK------			FINAL HEIGHT
ID	**SEX**	**AGE(y)**	**HT(cm)**	**VEL(cm/y)**	**AGE(y)**	**HT (cm)**	**VEL(cm/y)**	**(cm)**
87	F	7.95	114.71	5.56	10.57	130.55	6.66	146.10
89	M	10.31	121.70	4.18	13.91	142.99	8.76	158.13
90	M	10.68	124.89	4.29	14.02	145.41	9.22	159.95
94	M	10.82	128.68	4.26	14.20	148.19	8.14	162.24
95	F	10.84	124.82	4.26	13.91	139.40	5.36	152.64
96	M	12.36	133.51	3.57	16.19	152.60	7.28	166.21
101	M	11.04	134.38	4.92	13.86	153.29	9.57	166.88
102	M	10.62	124.08	4.19	14.43	145.77	8.08	161.37
103	M	12.63	126.93	3.38	16.04	147.02	10.76	161.21
105	F	9.44	119.30	4.40	12.48	136.34	7.43	149.00
108	M	10.78	126.37	3.95	14.48	146.56	7.91	161.00
110	M	10.93	133.00	4.46	13.97	149.58	6.87	162.39
113	F	9.19	119.18	4.94	12.21	137.72	7.90	151.78
114	M	10.52	126.85	4.28	13.85	145.93	8.00	159.75
116	M	11.89	129.73	3.69	15.52	150.89	9.68	165.74
118	M	13.22	128.43	3.38	16.90	148.91	9.63	163.31
119	M	9.86	125.28	4.62	13.70	148.63	8.27	165.71
121	F	8.33	113.64	4.86	11.71	134.76	8.35	150.38
125	M	10.65	127.71	4.19	13.91	147.32	9.10	161.20
128	M	12.14	133.92	3.76	15.41	154.50	11.03	168.99
131	M	10.80	128.75	4.50	14.33	150.06	8.48	165.45
133	F	10.06	122.41	4.26	13.35	141.78	8.50	155.63
134	M	12.03	129.51	3.55	15.49	149.40	9.83	163.37
136	M	11.37	135.86	4.67	14.97	158.37	8.69	174.68
137	F	9.52	121.43	4.57	12.52	138.24	7.08	151.19
138	F	6.72	106.58	5.20	9.80	126.21	8.07	141.31
139	F	10.23	124.02	4.17	13.01	137.38	5.68	148.57

SHORT CHILDREN

		-------TAKE-OFF--------			-----PUBERTAL PEAK------			FINAL HEIGHT
ID	**SEX**	**AGE(y)**	**HT(cm)**	**VEL(cm/y)**	**AGE(y)**	**HT (cm)**	**VEL(cm/y)**	**(cm)**
140	F	10.37	122.75	4.01	13.85	141.42	7.49	154.92
142	M	10.55	125.10	4.29	14.23	146.66	8.37	162.13
144	F	9.71	120.53	4.14	13.16	138.68	6.95	152.21
145	M	9.78	122.95	4.84	13.51	149.10	10.63	167.59
146	M	9.42	121.44	5.10	12.77	145.42	10.50	162.49
148	M	11.31	132.54	4.21	14.79	152.59	8.22	166.98
150	F	8.51	114.03	4.92	11.39	130.48	6.81	144.06
151	M	10.13	124.31	4.48	14.73	151.01	7.83	170.65
152	F	8.18	115.95	5.46	11.40	136.22	7.45	153.17
154	F	7.69	112.63	5.56	10.94	134.19	8.10	151.36
155	M	11.34	124.63	3.58	15.57	147.74	8.75	163.98
156	F	9.35	119.09	4.27	12.71	137.87	7.57	151.63
158	M	12.05	131.22	3.82	16.23	154.78	8.73	171.39
159	F	10.35	127.62	4.54	13.36	146.23	8.76	159.62
161	M	10.62	128.19	4.37	13.96	147.99	8.40	162.25
163	M	11.28	130.08	4.13	15.18	151.34	7.49	166.83
164	M	10.04	125.38	4.42	13.50	146.60	8.90	161.77
165	M	9.99	124.06	4.29	13.29	147.65	12.47	164.24
169	M	10.20	126.57	4.90	14.22	151.14	7.85	169.76
172	M	9.50	120.75	4.43	13.11	143.71	9.54	159.98
175	M	11.32	124.64	3.72	14.94	145.93	9.78	160.88
177	M	9.24	117.23	4.89	13.16	139.59	6.80	157.98

CONTROL CHILDREN

		-------TAKE-OFF--------			-----PUBERTAL PEAK------			FINAL HEIGHT
ID	**SEX**	**AGE(y)**	**HT(cm)**	**VEL(cm/y)**	**AGE(y)**	**HT (cm)**	**VEL(cm/y)**	**(cm)**
202	M	9.71	138.36	5.40	12.82	160.61	9.83	176.80
205	M	7.28	124.22	4.41	11.63	152.52	10.08	172.47
206	F	9.54	136.44	4.72	12.09	150.10	6.18	161.97
207	F	9.10	130.29	5.06	11.71	145.98	7.32	158.53
208	F	10.08	134.78	4.93	12.76	149.66	6.38	162.75
209	F	10.86	141.79	4.39	13.20	152.69	5.03	164.42
210	F	7.35	126.57	6.31	10.18	145.75	7.39	165.40
212	F	10.67	137.52	4.28	13.55	152.93	6.92	164.58
213	F	9.12	130.96	5.41	12.02	148.84	7.19	164.14
214	F	8.66	126.45	5.78	11.65	147.46	8.78	163.79
216	F	11.03	138.06	4.12	14.25	155.98	7.87	168.90
219	F	8.92	134.19	5.26	11.62	151.41	7.97	164.81
220	M	10.21	135.55	4.73	13.48	157.12	9.63	172.51
221	F	8.51	133.33	5.92	11.23	153.16	9.26	168.35
222	F	8.93	126.93	4.30	12.45	148.56	9.21	163.90
223	M	9.70	145.53	5.42	12.72	169.13	11.76	185.85
224	F	8.23	123.31	5.45	11.04	140.73	7.19	155.75
225	F	9.36	130.04	4.89	12.25	148.69	8.87	162.29
226	M	9.90	143.00	5.32	13.15	164.34	8.34	180.68
227	M	11.52	145.91	4.49	14.82	166.70	9.24	181.51
228	F	8.82	130.19	5.89	11.50	148.68	8.24	163.80
231	M	9.89	144.76	5.48	13.20	169.08	10.24	186.68
232	M	10.91	149.21	5.15	13.91	169.86	9.57	184.82
233	F	9.65	129.98	3.96	13.03	147.50	7.04	160.34
234	M	10.82	139.41	4.13	14.03	160.07	10.54	174.58
235	M	10.22	136.47	3.97	13.92	159.08	9.85	174.97
236	F	9.26	132.86	5.70	12.29	153.01	7.97	169.54

CONTROL CHILDREN

		-------TAKE-OFF--------			-----PUBERTAL PEAK------			FINAL HEIGHT
ID	**SEX**	**AGE(y)**	**HT(cm)**	**VEL(cm/y)**	**AGE(y)**	**HT (cm)**	**VEL(cm/y)**	**(cm)**
239	M	9.09	135.07	5.62	12.75	160.88	9.15	180.32
240	M	11.43	146.28	4.59	14.69	168.09	10.19	183.51
241	F	5.81	117.62	4.98	9.77	144.12	9.38	163.27
242	M	9.65	135.47	5.87	12.63	158.79	10.86	175.71
246	M	12.40	156.20	4.65	15.34	174.05	8.25	187.13
247	F	8.65	129.27	5.31	11.80	149.30	7.87	165.09
248	F	11.32	136.58	3.97	14.51	153.38	7.27	165.59
249	F	8.31	122.82	5.05	11.62	142.31	7.01	158.37
250	M	11.16	139.64	4.44	14.66	162.15	9.77	178.07
253	M	9.65	141.77	5.48	12.37	160.91	9.35	175.10
254	F	9.65	134.24	4.83	12.21	149.86	7.98	161.56
255	F	9.33	131.12	5.30	12.50	151.23	7.78	167.17
259	F	10.77	136.12	4.25	13.91	151.90	6.07	164.63
261	M	10.39	143.67	5.19	13.14	161.00	7.86	174.49
262	F	6.67	116.88	5.46	10.71	142.92	7.79	163.95
263	M	12.76	147.13	3.78	16.39	164.58	6.31	177.62
266	M	10.39	138.34	4.81	13.77	159.89	8.79	175.57
267	F	8.50	129.33	5.18	11.71	149.55	7.91	165.23
269	F	8.85	133.46	6.02	10.95	147.43	7.44	160.47
270	F	10.54	136.71	4.88	13.06	150.85	6.59	162.77
271	M	12.01	147.89	4.54	15.28	167.79	8.46	182.19
272	M	10.42	143.18	5.06	13.70	165.15	9.24	181.13
273	F	7.99	127.64	6.17	10.85	148.19	8.52	165.19
274	F	7.48	118.32	5.77	10.66	141.08	9.14	158.43
275	F	9.35	127.47	4.49	12.30	143.44	6.75	155.94
276	M	10.44	145.68	4.70	13.56	166.50	9.89	181.29
277	M	10.32	140.28	4.96	13.67	163.35	9.98	179.82

CONTROL CHILDREN

		-------TAKE-OFF--------			-----PUBERTAL PEAK------			FINAL HEIGHT
ID	SEX	AGE(y)	HT(cm)	VEL(cm/y)	AGE(y)	HT (cm)	VEL(cm/y)	(cm)
278	M	12.75	151.49	4.12	16.24	171.48	8.31	185.76
279	M	11.46	137.92	4.36	14.68	159.46	10.74	174.60
280	M	10.10	130.17	4.21	13.56	151.29	9.28	166.23
281	F	8.92	135.36	6.02	11.46	153.40	8.53	168.03
282	F	10.04	140.80	5.73	12.89	160.42	8.46	175.91
283	F	9.25	127.53	4.92	12.26	144.53	6.59	158.98
285	M	12.02	145.20	3.84	15.64	164.91	8.07	178.91
287	F	9.84	131.42	4.46	12.41	147.09	8.71	158.35
288	M	9.42	138.18	5.30	12.93	161.57	8.70	179.15
291	M	11.91	148.41	4.08	15.07	166.73	8.62	179.74
292	M	10.66	142.59	5.17	13.80	164.30	9.62	180.02
294	M	10.26	137.90	4.73	13.76	160.15	8.92	176.24
295	F	10.50	141.42	4.96	12.72	153.12	5.65	165.93
296	M	8.88	128.42	5.35	12.57	155.13	10.21	174.37
301	M	10.80	138.26	4.45	14.43	159.56	8.06	175.08
302	M	10.66	141.79	4.33	13.68	161.48	10.27	175.34
303	M	8.58	134.49	5.01	12.52	163.73	11.57	184.34
305	F	8.77	132.27	4.96	11.22	147.42	7.96	158.90
308	M	10.81	143.68	4.83	14.21	166.98	10.21	183.52
309	F	9.23	135.49	5.90	11.92	152.65	6.96	169.95
310	M	9.90	136.53	4.79	13.12	159.61	11.26	175.87
312	F	8.62	126.81	5.44	11.60	145.62	7.48	161.25
313	F	8.70	125.00	4.80	11.61	143.16	8.44	156.50
314	M	10.26	134.99	4.97	13.86	158.03	8.55	175.06
316	M	8.68	132.78	6.01	12.28	160.10	9.91	180.59
319	M	10.06	132.31	4.35	13.61	153.71	8.70	169.02
321	F	8.86	128.81	5.23	11.90	148.81	8.59	163.82

CONTROL CHILDREN

		-------TAKE-OFF--------			-----PUBERTAL PEAK------			FINAL HEIGHT
ID	SEX	AGE(y)	HT(cm)	VEL(cm/y)	AGE(y)	HT (cm)	VEL(cm/y)	(cm)
322	F	9.51	128.93	4.52	12.05	144.32	8.46	155.45
323	M	10.30	141.67	4.75	14.08	166.03	9.09	183.58
324	M	9.52	127.52	4.98	13.36	153.64	9.65	172.41
328	M	9.86	143.63	5.66	12.87	164.98	9.16	181.09
330	F	9.17	136.45	5.81	11.50	151.41	7.19	165.35
332	M	12.37	142.60	3.74	15.85	160.47	7.33	173.29
333	F	7.56	123.06	5.51	10.74	144.78	8.73	161.32
334	M	10.77	144.88	4.70	13.72	163.37	8.73	176.77
338	F	7.62	125.82	5.27	10.80	145.97	7.80	161.87
340	F	9.52	136.70	5.19	12.23	152.68	6.82	166.53
343	M	10.67	145.30	5.47	13.44	164.71	9.31	179.10
346	M	11.64	141.28	4.25	15.51	163.07	7.77	178.92
347	M	9.04	136.96	5.39	12.66	164.74	11.46	184.45
348	M	11.75	153.10	4.64	15.47	175.52	8.13	192.00
350	F	8.15	126.13	5.88	11.04	145.84	8.06	162.23
351	M	10.14	147.36	5.46	13.48	169.74	8.50	186.92
352	F	9.21	127.62	4.85	12.59	147.63	7.47	163.07
354	F	9.37	129.89	4.71	11.71	142.34	6.09	153.30
355	M	10.55	147.56	4.98	13.46	167.47	9.81	181.74
356	F	8.42	136.37	7.06	11.02	156.16	8.32	176.21
358	M	9.79	132.32	4.48	12.98	154.20	11.04	169.59
359	F	8.63	130.67	5.87	10.77	143.88	6.49	159.66
360	M	12.99	148.60	3.82	16.37	164.51	5.99	176.68
363	M	12.55	148.15	4.11	16.11	165.75	6.14	179.54
364	M	8.05	125.32	5.47	12.03	154.42	10.16	175.51
365	M	10.38	140.19	4.69	13.74	162.07	9.44	177.69
368	F	9.28	134.59	5.29	12.23	153.37	7.92	168.09

CONTROL CHILDREN

		-------TAKE-OFF--------			-----PUBERTAL PEAK------			FINAL HEIGHT
ID	**SEX**	**AGE(y)**	**HT(cm)**	**VEL(cm/y)**	**AGE(y)**	**HT (cm)**	**VEL(cm/y)**	**(cm)**
370	M	11.04	147.72	4.46	14.34	170.06	10.79	185.79
371	M	9.82	140.98	4.80	13.02	163.28	10.61	179.05
372	M	9.96	140.02	4.96	13.40	162.36	8.81	178.72
373	M	9.66	136.91	4.72	13.12	159.49	9.43	175.63
375	M	10.06	144.01	5.18	13.41	169.50	11.73	187.49
376	M	9.86	139.30	5.36	13.00	162.06	10.22	178.48

APPENDIX E

Questionnaires used to determine environmental and social variables

Medical History - Parent Questionnaire RECRUITMENT

.....Sex..... Code .....

ol .....Started!..... Code .....

of birth .....

er's height ..... Centile ..... Date of birth .....

pation ..... Ethnic origin .....

er's height ..... Centile .....Date of birth .....Rubella Vaccination ----

pation ..... Ethnic origin .....

ital Status - - - - - - - - - - -

lngs: Sex Age Height (if known) Other information eg. Family Health Problems and Height.

er

1.

2.

3.

4.

hts:

weight ..... Gestation ..... (premature/full-term/late)

tal problems ..... Special care baby unit .....

opmental milestones ..... (early/normal/slow)

sses (Acute) ..... (Chronic) .....

(past) ..... (present) .....

al school .....

cal disabilities .....

habits (neonatal) ..... (infant) ..... (present) .....

information:

Asthma –
Allergies –
Eczema –
Hayfever –

nurse:

School doctor:
Blood card ☐
X-ray card ☐

Nearest centre
- - - - - - - -

.....School.....

asurement	2nd Measurement	3rd Measurement .....
..... Age	Date ..... Age	Date ..... Age .....
.....Weight.....	Height	Height .....
.....S.D.S.....	Centile .....S.D.S.....	Centile .....S.D.S....

ental Centile .....

CODING SHEET
PARENT QUESTIONNAIRE, 1994/5

HEADERS C1. ID No. ☐☐☐

C2. Version ☐.☐ B1. Gender ...

C3. Interview Date ☐☐☐☐☐☐

B2. BAS Date ..../..../.... B3. BAS Age ____.____ years

C4. Interviewee(s) ☐ B4. GHIND ...

DIRECTORY

C5. School ID ☐☐ C6. Date of entry ☐☐☐☐

C7. School/Cohort code ☐ C8. Number of schools ☐☐

C9. Handedness ☐ C10. Football teams ☐☐ and ☐☐

PARENT QUESTIONNAIRE

POSITION IN SOCIETY

B5. Group membership ... B6. Belief in class ...

B7. Number of classes ...

B8. Subjective class, own rating ...

C11. Subjective class, forced choice ☐

OCCUPATION

(Mother/Female partner)

C12. Employed? ☐ C13. Job 5 yrs ☐ C14. Hours ☐☐

C15. Income ☐☐

C16. Parental absence? ☐ If yes, ages ☐☐ to ☐☐ and ☐☐ to ☐☐

(Father/ Male partner)

C17. Employed? ☐ C18. Job 5 yrs ☐ C19. Hours ☐☐

C20. Income ☐☐ C21. Parental absence? ☐ If yes, ages ☐☐ to ☐☐ and ☐☐ to ☐☐

(Natural parent)

C22. Income ☐☐

FAMILY SITUATION - PARTNER

C23. Female's relationship ☐ C24. Male's relationship ☐

C25. Main parent(s) ☐

FAMILY STATUS

C26. Family status ☐☐ C27. Length of marriage ☐☐

C28. Length of previous marriage ☐☐

C29. Number of relationships ☐ C30. Reconstitution status ☐

FAMILY STRUCTURE

WGS Child

C31. Birth order ☐☐ C32. Age order ☐☐

C33. Height in cms. ☐☐☐.☐ C34.Height description ☐

C35. Clinic ☐ C36. Issue for child ☐

C37. Birth weight ☐☐☐☐ C38. Gestational age ☐☐

C39. Induced? ☐ C40. Birth normal? ☐ C41. Smoking? ☐

B9. Gestational status ... B10. Records ...

Other Children

C42. Children in household ☐☐

C43. Relationships: Full sibs ☐☐ Half-sibs ☐☐
Step-sibs and others ☐☐

C44. Girls ☐☐ Boys ☐☐

C45. Older children ☐☐ Girls ☐☐ Boys ☐☐

C46. Younger children ☐☐ Girls ☐☐ Boys ☐☐

C47. Taller children ☐☐ Girls ☐ Boys ☐

C48. Shorter children ☐☐ Girls ☐ Boys ☐

C49. Clinic-referred ☐ C50. Stature an issue ☐

B11. Miscarriages, etc. ... IF Yes, number ...

PARENTS

C51. Natural Mother's height ☐☐☐.☐ C52. Description ☐

C53. Build ☐ C54. Age, actual or band ☐☐

C55. Natural Father's height ☐☐☐.☐ C56. Description ☐

C57. Build ☐ C58. Age, actual or band ☐☐

C59. Female partner's height ☐☐☐.☐

C60. Height description ☐ C61. Build ☐

C62. Age, actual or band ☐☐

C63. Male partner's height ☐☐☐.☐

C64. Height description ☐ C65. Build ☐

C66. Age, actual or band ☐☐

C67. WGS Child's height cf. current parents ☐

C68. Overall Comparison in home background ☐

EDUCATION

C69. Natural mother's education: Age left FTE ☐☐

C70. Highest qualification ☐☐

C71. Natural father's education: Age left FTE ☐☐

C72. Highest qualification ☐☐

C73. Female partner's education: Age left FTE ☐☐

C74. Highest qualification ☐☐

C75. Male partner's education: Age left FTE ☐☐

C76. Highest qualification ☐☐

B12. HIGHEST EDUCATIONAL LEVEL ☐☐

HEALTH

C77. Present health ☐ C78. Previous health ☐

C79. Allergies ☐ If Yes, ages ☐☐ to ☐☐

C80. Asthma ☐ If Yes, ages ☐☐ to ☐☐

C81. Eczema ☐ If Yes, ages ☐☐ to ☐☐

C82. Hay Fever ☐ If Yes, ages ☐☐ to ☐☐

C83. Medication ☐

C84. Appetite ☐ C85. Fussiness ☐ C86. Change ☐

C87. Child care affected by parent's health? ☐

(Records) B13. GP ... B14. National Health No. ...

RESIDENCE

C88. Tenure ☐ C89. Value ☐☐ C90. Type of property ☐

C91. Neighbourhood ☐ C92. Length of tenure ☐☐

C93. Number of addresses ☐☐ C94. Number of rooms ☐☐

C95. OVERCROWDING INDEX ☐.☐☐ C96. Sharing a room ☐

BULLYING

C97. Parental report ☐

C98. If Yes, (a) At present ☐ (b) At secondary school? ☐

(c) At junior school? ☐