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TALL STATURE; MORBIDITY, MORTALITY AND TREATMENT OUTCOMES

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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"Everything is theoretically impossible, until it is done."
Robert A. Heinlein

To my beloved family

ABSTRACT

Tall stature is usually constitutional. In some cases excessive growth is caused by early puberty and in others by growth disorders such as Marfan syndrome or pituitary gigantism. Some individuals experience a substantial negative psychosocial impact from being tall which can cause them and their families to seek medical attention. Whether or not to reduce adult height is an ethical dilemma where the psychological benefits must be weighed carefully against possible health complications. For over half a century, adolescent boys and girls have been treated with high-dose sex steroids in an attempt to reduce their adult heights by inducing early growth plate closure. In the late 1990s, another treatment option was introduced, so called epiphysiodesis, where growth plate cartilage in the lower extremities was surgically destroyed to stop further growth in tall adolescents. The overall aim of this thesis was to evaluate health consequences of the two principally different methods to reduce further growth in extremely tall adolescents and to study how height affects health.

In paper I we performed a cohort study of the cancer risk in 369 women who were assessed for tall stature during their adolescence at Swedish university hospitals between 1973 and 1993 and were followed for a median period of 27 years. Approximately half of them were treated with a median daily dose of 500 μg ethinyl oestradiol and the rest were untreated. The odds ratio (OR) for developing melanoma in treated compared to untreated was 6.1 (1.04-∞). The ORs for overall tumours and breast cancer were increased, but the risk estimates were imprecise.

In paper II we studied the efficacy and safety of percutaneous epiphysiodesis, in 21 operated boys and girls who were followed until reaching adult height. When compared to prediction, adult height was reduced by 4.1+/-0.7 cm in treated girls ($P<0.001$) and 6.4 +/- 0.7 cm in treated boys ($P<0.001$), corresponding to a third of predicted remaining growth in both genders. No serious side effects were reported during follow-up.

In paper III, the extensive Swedish population registers enabled us to study how height was associated with cancer and mortality in a very large cohort of five and a half million Swedish men and women born 1938-1991. Hazard ratio (HR) for any cancer per 10 cm increase in height was 1.19 (1.18, 1.20) in women and 1.11 (1.10, 1.12) in men. All 15 specific cancer sites studied were positively associated with height, melanoma most strongly so with HR 1.39 (1.35, 1.43) in women and 1.32 (1.28, 1.36) in men. Cancer mortality was increased with height in both genders whereas a number of other specific death causes, including cardiovascular disease, were decreased with height. Overall mortality was not notably affected by height in women, HR 0.98 (0.97 - 0.99), but decreased in taller men, HR 0.91 (0.90 - 0.92).

In summary, this thesis contributes to the understanding of how an individual's health is affected by height per se as well as by different height reduction therapies. This knowledge can facilitate better management of individuals who seek medical attention for tall stature.

LIST OF SCIENTIFIC PAPERS

I. **Benyi E**, Kieler H, Linder M, Ritzén M, Carlstedt-Duke J, Tuvemo T, Westphal O, Sävendahl L. Risks of malignant and non-malignant tumors in tall women treated with high-dose estrogen during adolescence. *Horm Res Paediatr* 2014;82:89-96. doi: 10.1159/000360137

II. **Benyi E,** Berner M, Bjernekull I, Boman A, Chrysis D, Nilsson O, Waehre A, Wehtje A, Sävendahl L. Efficacy and Safety of Percutaneous Epiphysiodesis Operation around the Knee to Reduce Adult Height in Extremely Tall Adolescent Girls and Boys. *International Journal of Pediatric Endocrinology* 2010;2010:740629. doi: 10.1155/2010/740629

III. **Benyi E**, Linder M, Adami J, Kieler H, Palme M, Sävendahl L. Adult height associated with cancer risk and mortality in 5.5 million Swedish women and men. *Manuscript*

ADDITIONAL PUBLICATIONS (NOT INCLUDED IN THE THESIS)

Liu F, Hendriks AE, Ralf A, Boot A, **Benyi E**, Sävendahl L, Oostra B, van Duijn C, Hofman A, Rivadeneira F, Uitterlinden A, Drop S, Kayser M. Common DNA variants predict tall stature in Europeans. *Human Genetics* 2014;133:587-597. doi: 10.1007/s00439-013-1394-0

CONTENTS

LIST OF ABBREVIATIONS

ALS	Acid labile subunit
BMI	Body mass index
BMP	Bone morphogenetic protein
CBS	Cystathionine-beta-synthase
CNP	C-type natriuretic peptide
CNS	Central nervous system
EE	Ethinyl oestradiol
ER	Oestrogen receptor
FBN1	Fibrillin-1
FGD	Familial glucocorticoid deficiency
FGF	Fibroblast growth factor
FMR1	Fragile X mental retardation 1
FOXO3	Forkhead Box O3
FSH	Follicle-stimulating hormone
GH	Growth hormone
GHR	Growth hormone receptor
GHRH	Growth hormone-releasing hormone
GnRH	Gonadotropin-releasing hormone
GPER1	G protein-coupled oestrogen receptor 1
GWAS	Genome-wide association study
HR	Hazard Ratio
ICD	International Classification of Diseases
IGF	Insulin-like growth factor
IGFBP	IGF-binding protein
IHH	Indian hedgehog

IQR	Interquartile range
LH	Luteinizing hormone
MAS	McCune-Albright syndrome
MEN-1	Multiple endocrine neoplasia type 1
MPA	Medroxy progesterone acetate
NPR	Natriuretic peptide receptor
NSD1	Nuclear receptor binding SET domain protein 1
OR	Odds ratio
PHV	Peak height velocity
PR	Progesterone receptor
PTH-rP	Parathyroid hormone-related peptide
RR	Relative risk
SD	Standard deviation
SEM	Standard error of the mean
SHOX	Short stature homeobox
SIR	Standardized incidence ratio
SOX	Sry-related HMG box
TH	Target height

1 INTRODUCTION

1.1 GROWTH

The growth of all Swedish children is closely monitored by child welfare centres and school health services. Nutrition, psychological wellbeing, and various medical conditions can affect growth which is therefore considered as a good indicator of general health (Delemarre-van de Waal 1993). Growth has physical as well as psychological and social impacts on the health of children and adolescents.

1.1.1 The growth of a child

The growth patterns vary markedly during different periods throughout foetal life and childhood. Karlberg et al. introduced the ICP-model where postnatal growth is divided into three different stages reflecting different hormonal phases of the growth process: Infancy, Childhood and Puberty (Karlberg 1989).

1.1.1.1 Foetal growth

The size of a newborn child depends on many different factors including genetics, gestational age, the size of the mother and uterine growth potential, nutrition, maternal diabetes, blood pressure and smoking (Botton et al. 2010; Mariante Giesta et al. 2015). The fastest growth occurs in utero, especially between week 20 and 24 when the foetus grows with a rate of 2.5 cm per week (Kappy et al. 2005).

1.1.1.2 Growth in infancy

The first year of life is also characterized by fast growth. A child increases its height with on average 25 cm during the first year of life and approximately half of that the second year. Nutrition can influence growth significantly in the first two years of life. This period might be characterized by an increase (“catch-up”), or decrease (“catch-down”) in growth rate (Davies et al. 2014). At one year of age boys are generally 1.5 cm taller than girls although their height velocities thereafter are comparable.

1.1.1.3 Childhood growth

At two years of age, the child has usually found a more steady growth rate where they do not cross height centiles, and then follow this path until puberty (Davies et al. 2014). During this period, nutrition has less influence on growth whereas hormonal regulators such as growth hormone (GH), insulin-like growth factor-1 (IGF-1) and thyroid hormone are more important (Martin et al. 2015). The height velocity is approximately eight centimetres per year between the ages of two and six after which it slows down slightly. How height velocity varies with age is illustrated in girls and boys, respectively, in Figure 1 and Figure 2 (Tanner et al. 1985). A small growth spurt can occur sometime between six and eight years of age at adrenarche, when there is an increase in anabolic hormones released by the adrenal glands. Until puberty girls and boys grow in a similar pattern.

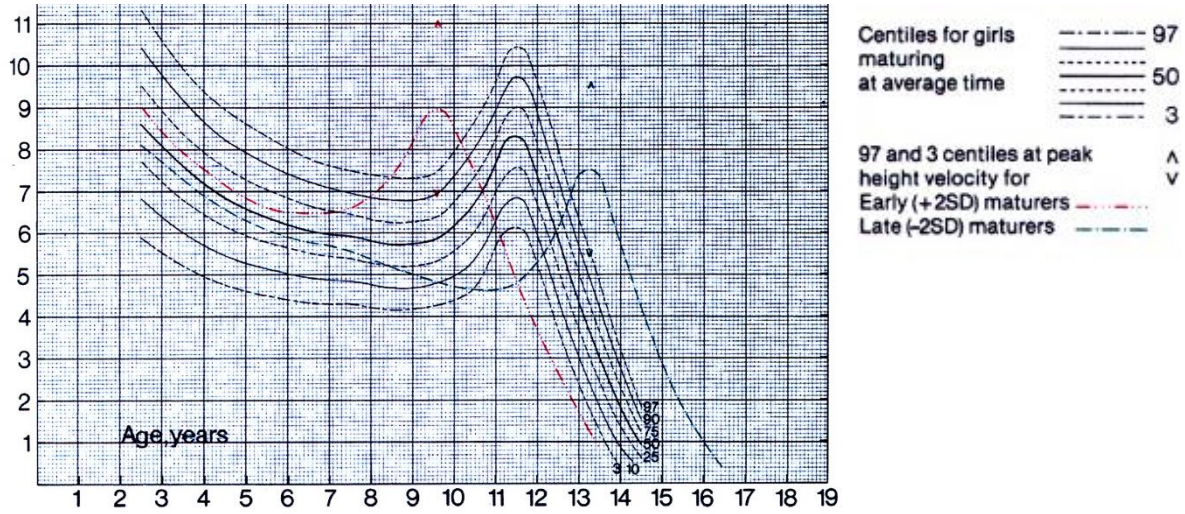

Figure 1. Height velocity in girls

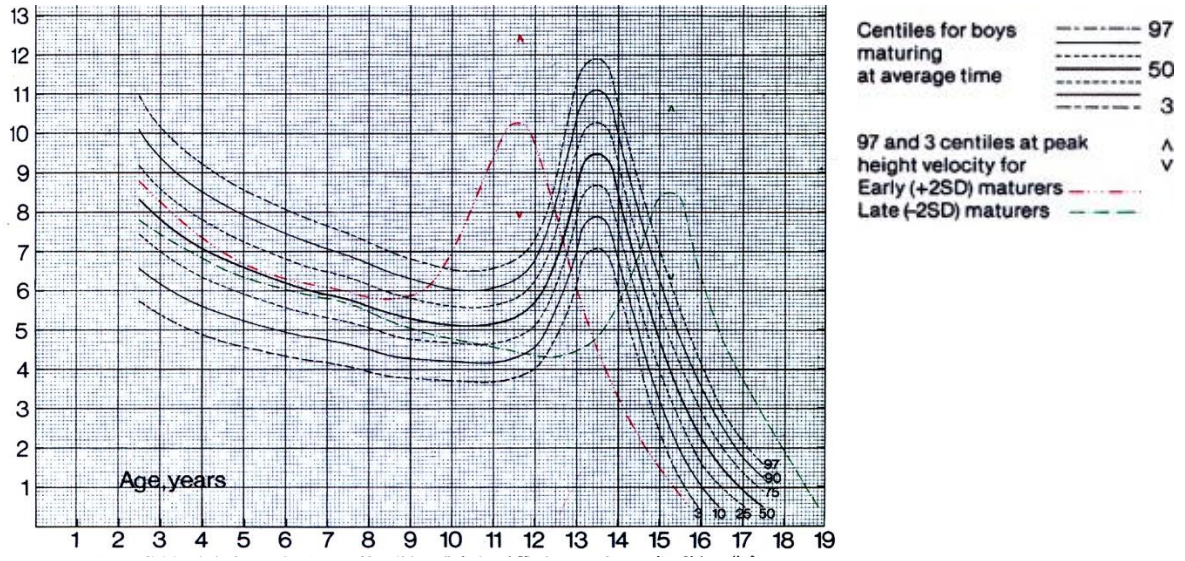

Figure 2. Height velocity in boys

Adapted from Tanner et al, 1985, "Clinical longitudinal standards for height and height velocity for North American children", The Journal of Pediatrics 107 (3), 317–29, with permission from Elsevier.

1.1.1.4 Pubertal growth

In Sweden, boys on average enter puberty at 12 years of age while girls enter on average one year earlier, generally with breast development as the first step (Ritzén 2003). During puberty, a growth spurt occurs in both sexes. In girls it starts in parallel with the onset of puberty whereas in boys it starts somewhat later. Feet and hands grow first, followed by arms and legs and at last, the spine. A recent study of 335 Polish children reported that the average age for the onset of the pubertal growth spurt was 10.0 years in girls and 11.9 years in boys (Limony et al. 2015). In a study of pubertal growth patterns in American children, girls on average reached a peak height velocity (PHV) of 8.3 cm/year at 11.5 years and boys a PHV of 9.5 cm/year at 13.5 years of age (Abbassi 1998). In Swedish children, an average PHV of 7.2 cm/year in girls was reached at 12.8 years and a PHV of 8.7 cm/year in boys at 14.3 years

of age, in two studies by the same author (Albin et al. 2012; Albin et al. 2013). Generally when height velocity starts to decline, menarche follows in girls. Typically, girls continue to grow another two years after menarche although it is highly variable. The pubertal height increment is approximately 30 cm, slightly higher in boys than in girls. However, there is a large individual as well as ethnic variation in pubertal development and growth pattern, including timing and tempo (Abbassi 1998).

1.1.2 The growth plate

The anlagen to all bones in the body are formed in utero. Long bones are developed in a process called endochondral ossification. Mesenchymal stem cells condensate and develop into a hyaline cartilage model. In this model, a primary ossification centre forms in the shaft of the bone. After vascularization of the primary ossification centre, secondary centres of ossification form in the epiphyses. In between the primary and secondary ossification centres near the ends of the long bones a thin remnant of cartilage is localized; the growth plate or epiphyseal plate (Figure 3), where all further longitudinal bone growth takes place. The growth plate is made up of the resting zone, the proliferative zone and the hypertrophic zone (Figure 4). Stem-like cells are recruited from the resting zone to start proliferating by mitosis (regulated by GH). In the proliferative zone, the chondrocytes get stacked in columns and proliferate at a high rate. In the hypertrophic zone the cells undergo hypertrophy and secrete extracellular matrix proteins which eventually become calcified. The terminal hypertrophic cells located near the metaphysis then undergo apoptosis and the remaining lacunae are invaded by bone-forming cells. Thereby, the diaphysis increases in length and hence, elongation of the long bone occurs (Mackie et al. 2008). When linear growth is completed and final height is reached, the growth plates close and all that remains is an epiphyseal line visible on X-ray that later disappears.

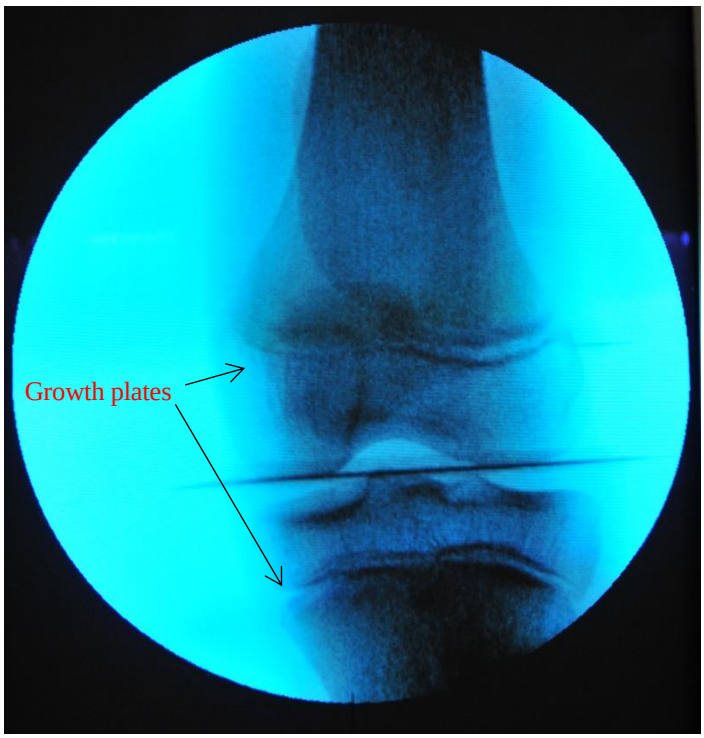

Figure 3. X-ray image of femoral and tibial growth plates. The femoral and tibial growth plates are marked with arrows.

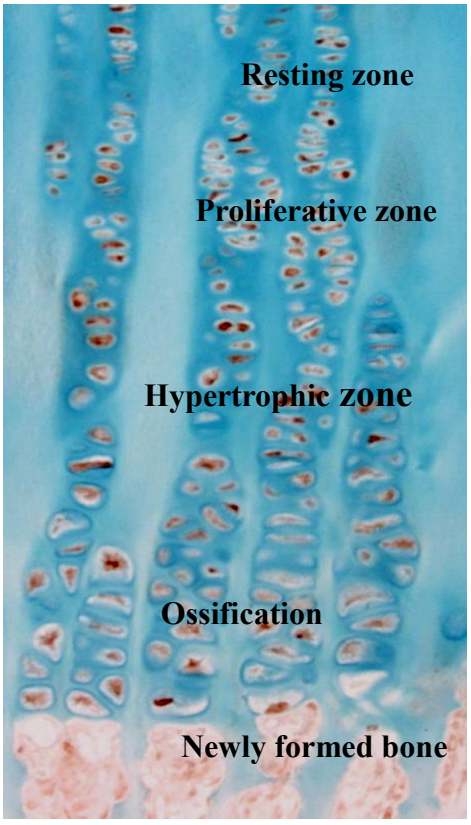

Figure 4. Growth plate zones. This figure illustrates the different zones in a sectioned human growth plate.

1.1.3 Growth regulation

Many signalling pathways, local and systemic, have been demonstrated to regulate longitudinal bone growth (Kronenberg 2003; X. Wang et al. 2015). Systemic factors include GH, insulin-like growth factors (IGFs), insulin, thyroid hormone, sex steroids, vitamin D and glucocorticoids. Local regulators include fibroblast growth factor (FGF), bone morphogenetic proteins (BMPs), parathyroid hormone-related peptide (PTHrP), Wingless-type MMTV integration site family (Wnt), Indian hedgehog (IHH), IGFs, and retinoids. Some of these important regulatory pathways are described in detail below.

1.1.3.1 Growth hormone and IGF-1

Growth hormone is a single polypeptide chain made up of 191 amino acids produced by the pituitary gland. Two GH-genes on chromosome 17 have been discovered (Camacho-Hübner 2000). GH exerts its action by binding to the growth hormone receptor (GHR) which is abundantly expressed in most tissues. The GHR is a transmembrane receptor belonging to the cytokine receptor family. Growth hormone stimulates longitudinal bone growth both via direct stimulation of the growth plate, and indirectly via IGF-1.

Insulin growth factor-1 is a polypeptide encoded by the Igf-1 gene on chromosome 12 (Camacho-Hübner 2000). It is structurally homologous with proinsulin. Circulating IGF-1 is mainly produced in the liver but IGF-1 is also ubiquitously expressed in many other tissues such as fat and muscle. Insulin growth factor-1 is also produced in the growth plate, thereby acting in a paracrine/autocrine fashion under the influence of GH (Shim 2015). In the circulation, IGF-1 is bound to IGF-binding proteins (IGFBPs), mainly IGFBP-3, and the acid labile subunit (ALS) forming a ternary complex. Insulin growth factor-1 is believed to stimulate linear growth, both systemically as well as locally in the growth plate (Baxter 1988).

Growth hormone has anabolic effects on many tissues, e.g. skeletal muscles and bone. It is not only important for bone growth during childhood and puberty but it also affects bone mineral density and is essential for metabolism. Growth hormone stimulates growth principally through two different pathways (Figure 5): 1) by binding to GHR on target cells in the growth plate and thereby stimulating chondrogenesis, 2) by stimulating the hepatic production of IGF-1. Growth hormone itself is mainly regulated by two peptides secreted by the hypothalamus, growth hormone-releasing hormone (GHRH) and the inhibitory hormone somatostatin. It is also stimulated by ghrelin produced in the stomach and IGF-1 exerts negative feedback control (Meinhardt et al. 2006).

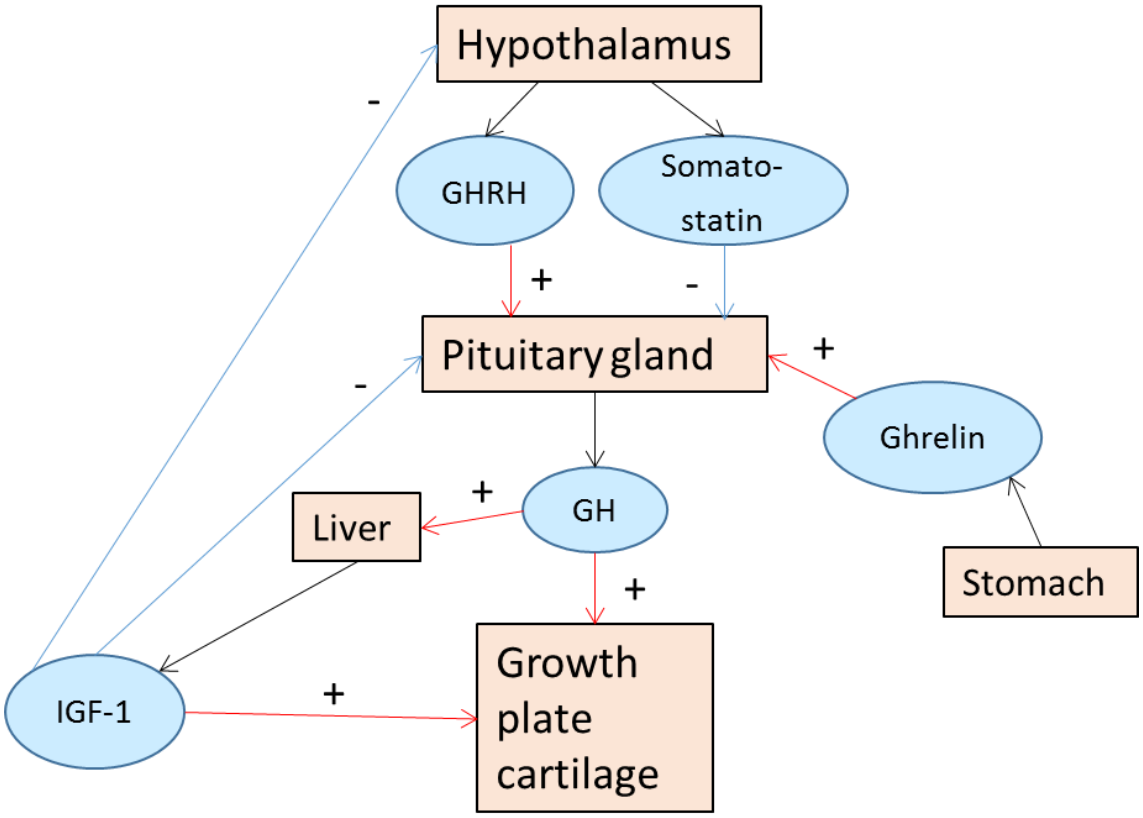

Figure 5. The GH/IGF-1 axis. This diagram illustrates a basic overview of the GH/IGF-1 axis with focus on bone growth regulation.

It has previously been suggested that local effects of IGF-1 in the growth plate are more important than its endocrine effects for stimulating longitudinal bone growth (Wit et al. 2011). However, a recent knock-out study in mice lacking the IGF-1 receptor exclusively in the growth plate showed that GH can stimulate chondrogenesis and longitudinal bone growth even when local IGF-1 and IGF-2 action is inactivated (Wu et al. 2015). Insulin growth factor-1 stimulates protein synthesis through the uptake of amino acids from the circulation. It also stimulates both proliferation and hypertrophy of chondrocytes as well as ossification by affecting the osteoblasts. Insulin growth factor-1 increases bone mineral density and also muscle mass and lipolysis in fat tissue (Yakar et al. 2015). Serum concentrations of GH and IGF-1 can be increased more than 3-fold during puberty.

Underproduction of GH can lead to short stature in children. Overproduction, on the other hand, can lead to gigantism in children (1.5.1) and acromegaly in adults. In the latter, the bones in the face, hands and feet continue to grow in the adult. Growth hormone deficiency appears to mainly affect postnatal growth whereas IGF-1 deficiency affects both prenatal and postnatal growth (Yakar et al. 2015). Insulin growth factor-2 is another polypeptide in the same family that also affects pre- and, to a lesser extent, postnatal growth although IGF-1 is the predominant regulator of postnatal growth (Begemann et al. 2015).

1.1.3.2 Sex steroids

Sex steroids including oestrogen and testosterone are mainly produced by the gonads. Oestrogens play an important role for growth in both girls and boys. In girls oestrogens are mainly produced in the ovaries. There is also oestrogen production in the testes although the main production in boys occurs in peripheral tissues by aromatizing androgens (Figure 6). This is mediated by the converting enzyme aromatase, or CYP450, which can be found in many different tissues including gonads, brain, fat tissue, placenta as well as the growth plate where oestrogen appears to be synthesized locally (Oz et al. 2001; Hess 2003). The three major endogenous oestrogens are oestrone, oestradiol and oestriol (Xu et al. 2007). Except for pregnancy when oestriol is the primary oestrogen, oestradiol is the most common oestrogen in women until menopause when instead oestrone will dominate.

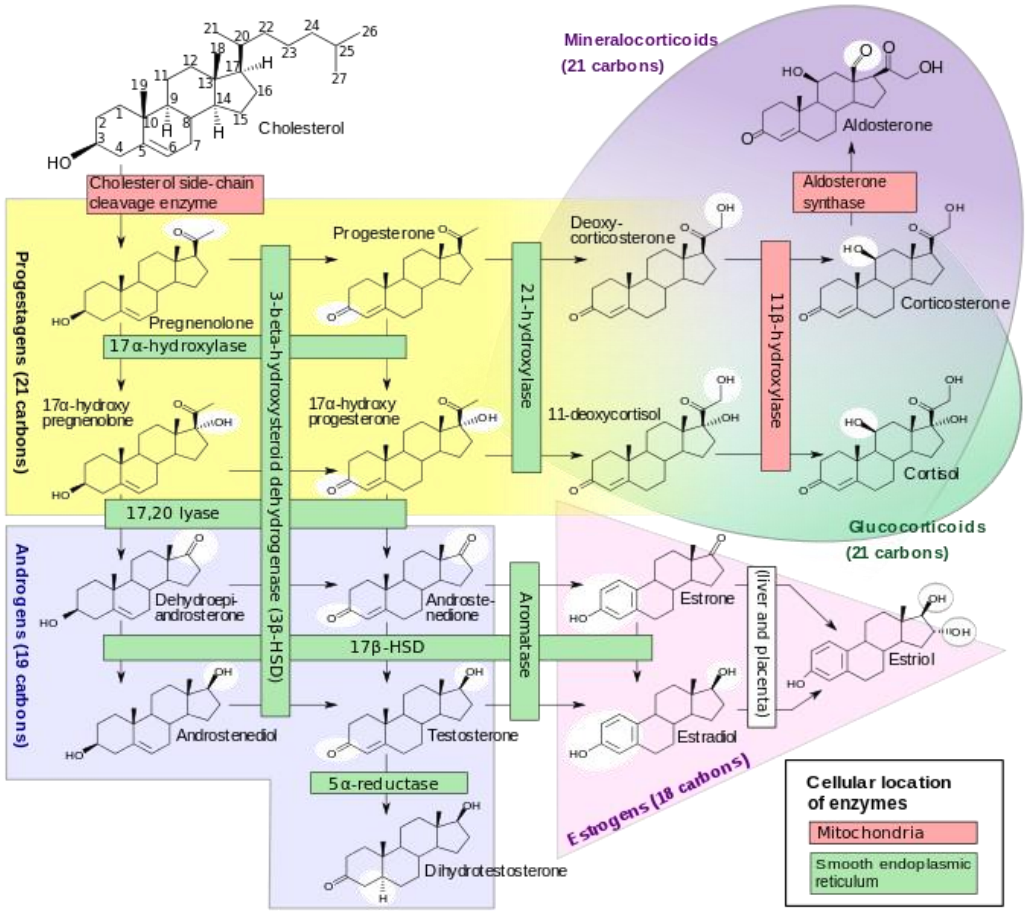

Figure 6. Biosynthesis of sex steroids. Reproduced from Häggström et al, 2014, "Diagram of the pathways of human steroidogenesis", Wikiversity Journal of Medicine 1 (1), DOI:10.15347/wjm/2014.005. ISSN 20018762, licensed under Creative Commons.

Puberty is characterized by an activation of the hypothalamic-pituitary-gonadal axes (Rogol 2004). Gonadotropin-releasing hormone (GnRH) pulses trigger the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary which stimulates sex hormone release from the gonads. An increase in GH pulse amplitude before pubertal onset in girls and somewhat later in boys has been shown (Rose et al. 1991). It was recently

reported that also IGF-1 levels during puberty correlate closely with PHV (Cole et al. 2015). Oestrogens affect growth by regulating the effect of GH and its secretion by reducing IGF-1 mediated negative feedback (Meinhardt et al. 2006). Delemarre-van den Waal concluded that oestradiol and GH regulate pubertal growth in both girls and boys and in addition puberty is regulated by androstenedione in girls and testosterone in boys (Delemarre-van de Waal et al. 2001). Testosterone increases the effect of GH on IGF-1 secretion. Androgen receptors are present in the human growth plates as well as in those of rodents, but any local direct effects on longitudinal growth by androgens were not found in foetal metatarsals from rats (Chagin et al. 2009). Oestrogens, although stimulating growth during puberty, is the factor that finally leads to growth plate fusion at the end of puberty in both genders (Börjesson et al. 2012).

Oestrogens act by binding two different nuclear receptors in the growth plate, oestrogen receptor (ER)α and ERβ, and a more recently discovered G protein-coupled oestrogen receptor 1 (GPER1) which is membrane-bound and was previously called GPR30 (Thomas et al. 2005; Chagin et al. 2007). ERα and ERβ are both expressed in the different zones of the growth plate (Nilsson et al. 2003). The abundance of both receptors increases as the cells differentiate (Simm et al. 2011). Oestrogens stimulate osteoblasts and inhibit osteoclasts but the exact mechanisms through which they promote bone growth are not clear (Rochira et al 2015). The two receptors have been studied in knock-out mice. Inactivation of ERβ but not ERα stopped growth plate fusion (Chagin et al. 2004). ERα inactivation has been shown to decrease bone growth in mice (Parikka et al. 2005; Chagin et al. 2004). ERβ inactivation affected growth in some studies but not in others and differences between male and female mice in the effects of ERα and ERβ inactivation on bone growth have been observed (Sims et al. 2002; Windahl et al. 1999; Chagin et al. 2004). Simm et al concluded that ERα stimulates different steps of chondrogenesis whereas ERβ inhibits skeletal growth in mice (Simm et al. 2011). The receptor GPER1 is highly expressed in the hypertrophic zone especially before puberty when it starts a gradual decrease, suggesting a role in longitudinal bone growth regulation (Chagin et al. 2007).

There are important differences between mice and humans to consider when interpreting mouse data. For example, a pubertal growth spurt is lacking in mice and their growth plates do not fuse after sexual maturation as they do in humans. Observations in mice suggest that ERβ is important for growth plate fusion in mice. However, open growth plates at 28 years of age were observed in a male patient (the so called "hERKO man") who had an ERα inactivating mutation (Smith et al. 2010). He was 204 cm tall and had reduced bone mineral density. More recently, an ERα mutation was also described in an 18 year old woman who appeared to have a complete oestrogen insensitivity with lack of breast development and elevated serum oestrogen levels (Quaynor et al. 2013). Patients with aromatase deficiencies exhibit similar phenotypes with a lack of pubertal growth spurt and growth plates which remain open in adulthood leading to tall stature. However, a patient with aromatase deficiency will respond to oestrogen treatment whereas such therapies will have no effect on bone mineral density and bone maturation in an ERα-mutated patient (Zirilli et al. 2009; Smith et al. 1994).

1.1.3.3 Glucocorticoids and inflammation

Both glucocorticoids and proinflammatory cytokines may impact growth negatively by affecting chondrogenesis (Sävendahl 2012). Growth retardation has been observed in children who are treated with glucocorticoids for different conditions (Ribeiro et al. 2015; De Boeck et al. 2007). The mechanisms are not clear but it has been shown that glucocorticoids decrease proliferation as well as induce apoptosis of the chondrocytes in the growth plate (Chrysis et al. 2003). Local effects in the growth plate were demonstrated by infusion of Dexamethasone into tibial growth plates in rabbits which significantly reduced the growth rate (Baron et al. 1992). Patients with familial glucocorticoid deficiency (FGD) associated with adrenocorticotropic hormone (ACTH) resistance exhibit tall stature (Elias et al. 2000).

1.1.3.4 Fibroblast growth factors

Fibroblast growth factors (FGFs) have important roles at every stage of endochondral bone formation. The best understood FGF receptor is FGFR3 which is a negative regulator of endochondral ossification (X. Wang et al. 2015). Gain-of-function mutations in this gene lead to genetic skeletal disorders such as achondroplasia which is the most common genetic form of dwarfism in humans. FGF-1 has also been reported to be growth-inhibiting whereas FGF-2 has been reported to be growth-promoting (Lazarus et al. 2007).

1.1.3.5 Bone morphogenetic proteins

Bone morphogenetic proteins (BMPs) are also called growth and differentiation factors and similar to FGFs they are important throughout the endochondral ossification process although in some of the stages, FGFs and BMBs seem to have antagonizing effects (Niswander et al. 1993).

1.1.3.6 Parathyroid hormone-related peptide

Parathyroid hormone-related peptide (PTHrP) binds to the same receptors as parathyroid hormone. It has a stabilizing role in the growth plate by maintaining chondrocytes in a proliferative stage and inhibiting hypertrophy. Mutations of PTHrP or its receptors lead to short limbs by affecting chondrocyte maturation (Späth et al. 2011).

1.1.3.7 C‑type natriuretic peptide

C‑type natriuretic peptide (CNP) has a positive regulatory function locally in the growth plate (Pejchalova et al. 2007). Inactivating mutations of its receptor, the natriuretic peptide receptor (NPR)2, can cause skeletal dysplasia's and short stature whereas CNP activating mutations or overexpression of CNP can cause tall stature (Wang et al. 2015; Hannema et al. 2013).

1.1.3.8 Other local factors

Local factors affecting proliferation and differentiation of chondrocytes include Sry-related HMG box (SOX)9 which stimulates the converting of stem cells into the chondrocyte

lineage, and IHH which stimulates PTHrP and chondrocyte differentiation (Akiyama et al. 2002; Kobayashi et al. 2005).

1.2 TALL STATURE- OVERVIEW

Extreme tall stature is commonly defined as a height exceeding three standard deviations (SD) above the mean, which corresponds to approximately 200 and 185 cm, respectively, for Swedish men and women. This means that three in one thousand of the Swedish population have heights above these values. Even though tall stature is in the vast majority of cases constitutional, growth disorders causing excessive growth are important to rule out in patients seeking medical attention for tall stature, since they can be associated with other health implications. There is a common division into primary and secondary growth disorders. Primary growth disorders affect the growth process itself and may have a prenatal onset. Secondary growth disorders are caused by external factors and affect growth indirectly. Most commonly they are caused by hormonal disturbances (Drop et al. 2001). A suggestion of the investigation procedure is shown in Figure 7 (Davies et al. 2014).

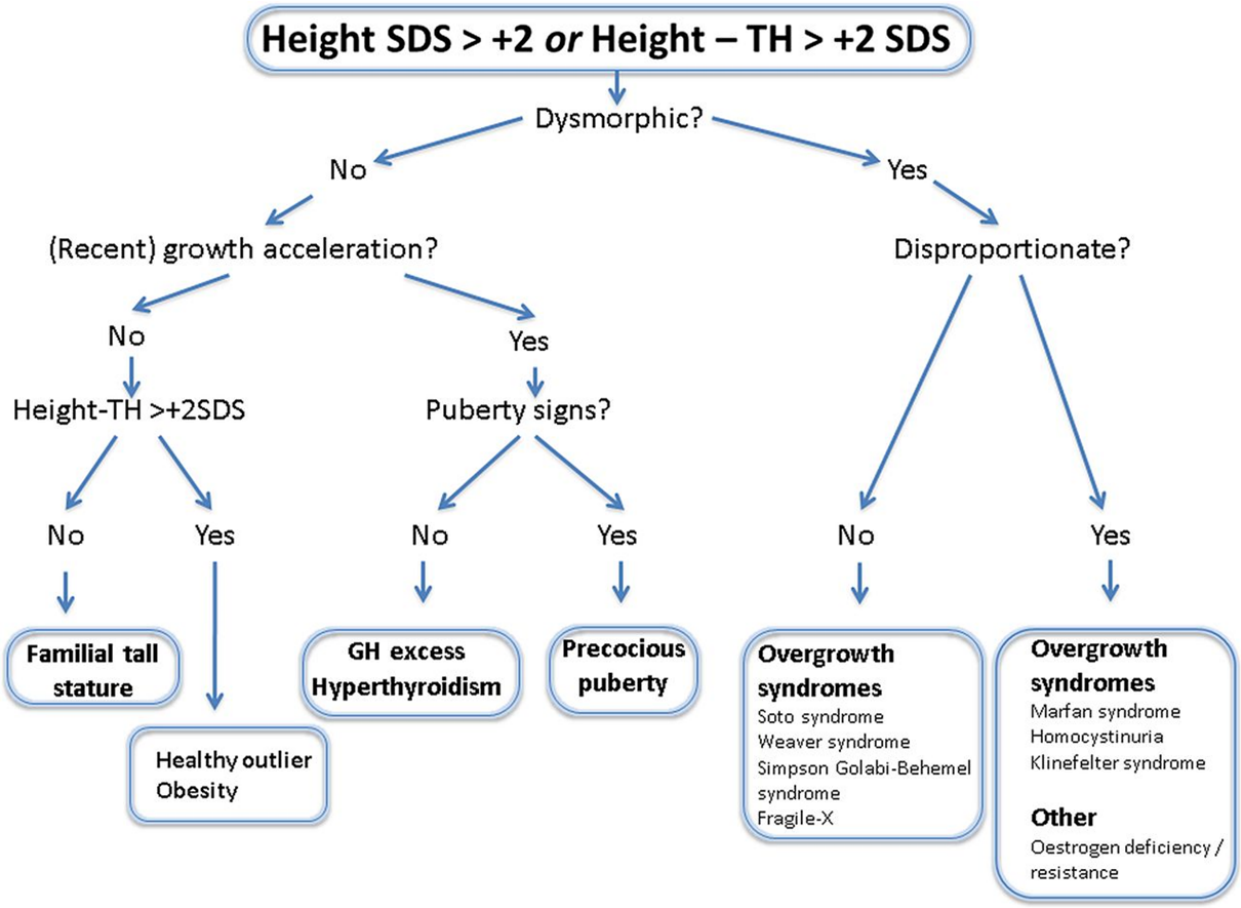

Figure 7. Diagnostic approach to tall stature. Reproduced from Davies et al, 2014, Archives of Disease in Childhood, 99 (8), 772–77, with permission from BMJ Publishing Group Ltd.

1.3 CONSTITUTIONAL TALL STATURE

Constitutional tall stature is also known as familial tall stature. It is genetic, hence depending on the height of the mother and father of the child. Height is highly heritable in a polygenic manner. It was estimated in a sibling study that the heritability of height is 80% (Visscher et al. 2006). Through genome-wide association studies (GWAS) over 400 loci associated with height have been identified, explaining approximately 20% of the phenotypic and 25% of the genetic height variation (Lango et al. 2010; Wood et al. 2014). Elevated levels of GH and IGF have been observed in studies of individuals with constitutional tall stature but the results are inconclusive (Albertsson-Wikland et al. 1988; Garrone et al. 2002; Tauber et al. 1994; Stratakis et al. 1996).

Constitutionally tall children often grow more rapidly in the first four years of life, after which growth rate drops to normal (Dickerman et al. 1984). Dickerman et al. studied the growth patterns from birth to nine years of age in 65 children diagnosed with constitutional tall stature. Their mean birth heights were 52.1 and 53.5 cm in girls and boys, respectively, corresponding to the 75^{th} percentile. At four years of age, their heights had increased to 111.7 and 113.0, respectively, corresponding to 2.5 SD above the mean. Between four and nine years, the growth curves were parallel with the 50^{th} percentile, but 2.75 SD above on average. The authors suggest that the fact that the birth length does not deviate from normal indicates that factors leading to tall stature are postnatal.

1.4 PRIMARY GROWTH DISORDERS

1.4.1 Marfan syndrome

Marfan syndrome is a connective tissue disorder cause by a mutation in the Fibrillin-1 (FBN1) gene located on chromosome 15 (15q21.1). This gene encodes a glycoprotein called fibrillin-1 which is essential for connective tissue formation. Marfan syndrome affects approximately two to three per 10,000 individuals (Judge et al. 2005; Groth et al. 2015). It is usually inherited in an autosomal dominant pattern even though approximately 25% of affected individuals have a de novo-mutation. The most serious abnormality associated with this syndrome is dilatation of the aorta which can lead to aortic dissection and rupture, a fatal condition. Other clinical features include ectopia lentis, scoliosis, crowded teeth as well as flexible and painful joints. Children with Marfan syndrome may grow extremely tall with especially long arms, legs, fingers and toes. In 1986, an expert panel developed a set of diagnostic criteria, called the Berlin Nosology, aimed to facilitate accurate diagnosis (Beighton et al. 1988). This was later revised due to overdiagnosis and the commonly used Ghent criteria were developed (De Paepe et al. 1996), with further revisions in 2010 (Loeys et al. 2010). These diagnostic criteria are mainly focused on the family history of Marfan, ectopia lentis, aortic dilatation and FBN-1 mutations. Additional criteria include body disproportions and musculoskeletal abnormalities.

1.4.2 Klinefelter syndrome

Klinefelter syndrome, also called 47,XXY, affects one to two boys in a thousand (Davies et al. 2014). Due to an extra X-chromosome, these patients have excess expression of certain genes. One of these is the short stature homeobox (SHOX) gene, which has been shown to influence the phenotype seen in Klinefelter syndrome (Groth et al. 2013; Tüttelmann et al. 2010). Clinical features include tall stature, small genitalia, muscle weakness, cognitive disabilities, infertility and gynecomastia. Affected boys also have a higher risk of developing diabetes mellitus, cancer and cardiovascular disease. Klinefelter syndrome is often diagnosed late, when affected men try to conceive (Bar et al. 2014).

1.4.3 Homocysteinuria

Homocysteinuria is an autosomal recessive disorder caused by a mutation in the cystathionine-beta-synthase (CBS) gene on chromosome 21 (21q22.3) affecting approximately one in 6000 newborn children (Refsum et al. 2004). Individuals with homocysteinuria have a deficient elimination of homocysteine and its metabolites. There are two types, B_6-responsive and B_6-nonresponsive homocysteinuria, the first usually being milder than the second. Homocysteinuria affects connective tissues in the body, including fibrillin. Affected individuals may exhibit clinical features similar to those in Marfan patients including tall stature with long legs and arms, scoliosis and ectopia lentis. They might also suffer developmental delay (especially the B_6-nonresponsive type) and thromboembolic complications which can lead to an early death (Picker et al. 1993).

1.4.4 Fragile X

Fragile X affects approximately one in 5000 males and one in 10,000 females and is caused by a mutation in the fragile X mental retardation 1 (FMR1) gene located on the X-chromosome. Symptoms include tall stature, mental retardation, autism and a characteristic appearance with a protruding forehead and large ears (Saldarriaga et al. 2014).

1.4.5 Sotos syndrome

Sotos syndrome affects one in 10,000 to 14,000 newborns and is caused by mutations in the nuclear receptor binding SET domain protein 1 (NSD1) gene in 90% of the cases. Affected individuals have an increased height velocity during the first four years of life and an increased adult height. Cognitive disabilities are common (Sheth et al. 2015).

1.5 SECONDARY GROWTH DISORDERS

1.5.1 Pituitary gigantism

Pituitary gigantism causes abnormal growth in childhood due to excessive secretion of GH. The most common cause is a benign pituitary tumour but the incidence is unknown (Eugster et al. 1999). In some cases underlying causes are Carney complex, McCune-Albright

syndrome (MAS), Multiple endocrine neoplasia type 1 (MEN-1) and Neurofibromatosis (Christoforidis et al. 2006; Rostomyan et al. 2015). Pituitary gigantism causes bones as well as muscles and internal organs to grow excessively. Other physical features associated include frontal bossing, a prominent jaw, large hands and feet. It can also cause delayed puberty, headaches, muscle weakness, double vision and sleeping problems. Different treatment methods are available including transsphenoidal surgery, somatostatin analogues and GH antagonists (Sotos et al. 2008).

1.5.2 Obesity

Obese children often experience tall stature due to early adrenarche, early puberty and advanced skeletal maturation. The mechanism is thought to be hyperinsulinemia. Insulin binds to the IGF-1 receptor and increases height velocity. It also increases free IGF-1 in the circulation (Sotos and Argente 2008). However, adult height is usually not affected due to a more blunted pubertal growth spurt and earlier epiphyseal closure (He et al 2001).

1.5.3 Hyperthyroidism

Thyrotoxicosis in childhood may cause an acceleration of skeletal maturation and linear growth. It is unclear whether this acceleration affects the final height or if is compensated by a hasted bone maturation (Wong et al. 1999; Wit et al. 2011).

1.5.4 Precocious puberty

Children are considered to experience premature puberty if entering before eight years of age for girls and nine years for boys (Berberoğlu 2009). Precocious puberty affects approximately one in 500 girls and one in 2000 boys (Teilmann et al. 2005). These girls and boys are tall during childhood, but due to the advancement in skeletal maturation and early growth plate fusion, adult height is usually unaffected or if left untreated- sometimes decreased (Sotos et al. 2008; Davies et al. 2014).

1.6 OTHER RARE DISORDERS

There are a number of other rare conditions not discussed in detail in this thesis, which can cause tall stature. These include familial glucocorticoid deficiency (FGD), Trisomy X, aromatase deficiency, oestrogen resistance, androgen insensitivity, Simpson-Golabi-Behmel syndrome, Weaver syndrome, Lhermitte-Duclos syndrome, Bannayan-Riley-Ruvalcaba syndrome, Nevo syndrome, Loeys–Dietz syndrome, Perlman syndrome and Cowden disease (Neylon et al. 2012; Sotos et al. 2008).

1.7 HEIGHT PREDICTION

1.7.1 Prediction based on midparental height

An individual's height is usually genetic, in other words determined by the parental heights. Different calculations have been proposed to predict an individual's adult height from the parental heights. It is generally referred to as "target height (TH)". Probably the most common method is the so called "Tanner method" developed in 1970 which uses a sex-corrected midparental height (Tanner et al. 1970) :

TH (cm) = (mothers height + fathers height)/2 – 6.5 for girls and + 6.5 for boys

1.7.2 Prediction from radiologically assessed bone age

From an X-ray image of the left hand and wrist, the degree of skeletal maturation can be assessed by determining the bone age using the atlas of Greulich and Pyle (Pyle et al. 1971). This information is of great value when evaluating both tall and short stature. It can be used to estimate the remaining growth for the patient with different methods including the Bayley and Pinneau tables (Bayley et al 1952), Tanner Whitehouse (Tanner et al. 1983), and clinical assessment taken into consideration factors such as pubertal stage. De Waal et al. evaluated different methods and concluded that the precision of height predictions was clinically acceptable in girls but not in boys. In both girls and boys the Bayley and Pinneau and the clinical methods overestimated while Tanner Whitehouse underestimated final height. The absolute error was on average approximately 2 cm in girls and 3 cm in boys for each of these three methods (de Waal et al. 1996).

There are also automated options of bone age determination from X-ray images including the commercial product BoneXpert (Visiana, Denmark) (Thodberg et al. 2009). This software has been found to be reliable in several different patient groups, resulting in predictions similar to those made by clinicians (Khan et al. 2015; D. D. Martin et al. 2011).

1.8 ASSESSMENT OF THE TALL CHILD

When a child presents for evaluation of tall stature it is important to establish whether it is the child or the parents who are concerned. A thorough patient history and physical examination is essential. Also children with heights close to average might need investigation if their heights are well above their midparental target height or if they experience a sudden growth acceleration. Some conditions can cause excessive growth during childhood with a normalization of height before adult age, such as obesity and precocious puberty.

Auxological measurements should include total height as well as sitting height and arm span. Sitting height percentage is usually calculated as the proportion of the upper body segment compared to total height (including the lower extremities) and references are shown in Figure 8 (Fredriks et al. 2005). Patients with Klinefelter or Marfan syndrome usually have disproportionally long legs and arms. Body mass index (BMI) should be calculated and

pubertal staging performed including measurement of testicular volumes in boys. Bone age can be determined from an X-ray image of the left hand and wrist to assess the status of skeletal maturation (section 1.7.2). This should not be done until the patient has entered puberty as final height prognoses based on bone age are unreliable prior. Table 1 shows initial investigation at the primary care level.

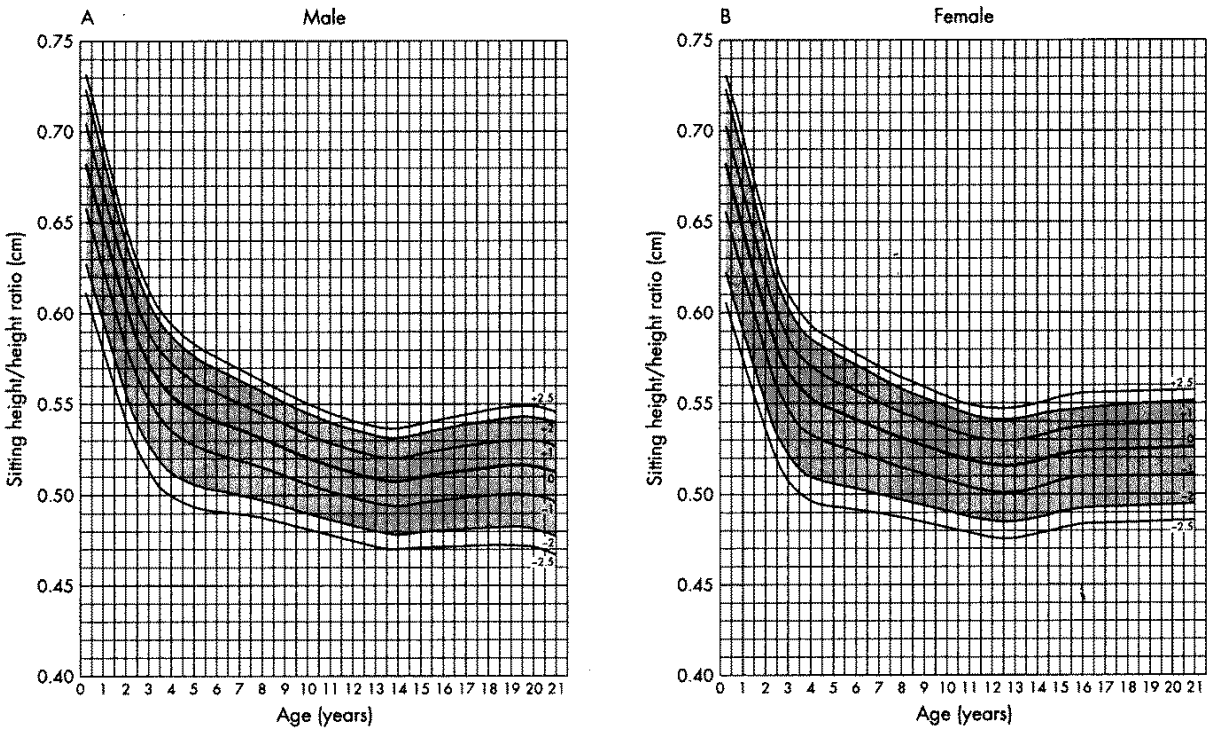

Figure 8. Sitting height percentage. Reproduced from Fredriks, A et al, 2004, Archives of Disease in Childhood, 90 (8), 807–12, with permission from BMJ Publishing Group Ltd.

- Bone age X-ray (left hand and wrist); only of value for adult height predictione once the patient has entered puberty. State height of patient and parents in the referral
- Specific investigations including lab tests (normally not necessary) if suspicion of:
    - Homocysteinuria→ P-homocystein
    - Klinefelter syndrome→ Karyotype
    - Marfan syndrom→ Echocardiography and ophtalmology consultation
    - Gigantism/Acromegaly→ S-IGF-1, S-GH

Table 1. Workup at primary care level

Of vital importance is to exclude potentially serious conditions which might require treatment, such as Marfan syndrome. If Marfan is suspected, the patient should be referred to a paediatric cardiologist who performs echocardiography to assess any aorta dilatation which can lead to aortic rupture. In some cases clinical geneticists are consulted and genetic testing

can be used for diagnosis. Karyotyping is performed if for example Klinefelter syndrome is suspected. Some diagnoses can be confirmed with blood tests, for example pituitary gigantism (GH and IGF-1) and homocysteinuria (homocysteine). Table 2 indicates when referral to a specialist in paediatric endocrinology should be considered.

Consider referral if:

- Marked growth (but not weight) acceleration after one year of age
- Tall stature atypical for the family (height >2 SD over SD for target height)
- Patient's concern of extreme adult height; refer when a girl has reached a height of 165 and a boy has reached 180 cm

Information to include in referral:

Patient history

- Who initiated investigation?
- Growth chart of height and weight from birth until present
- Other health issues including back or joints problems, previous lens luxation
- Time of puberty onset and menarche (girls)
- Any difficulties in school

Hereditary factors

- Sudden deaths in the family
- Parental heights and timing of puberty

Physical examination

- Tanner puberty stage
- Testicle volume (boys)

Table 2. Referral to specialist

In the vast majority of cases, tall children will be diagnosed with constitutional tall stature. Reassurance is often sufficient in the management of the constitutionally tall patients and their families. In a few cases, an intervention might be called for (section 1.9). In the paediatric endocrine clinic at Karolinska University Hospital, a decision regarding height reduction therapy is taken earliest when girls have reached a height of 165 cm and boys a height of 180 cm.

1.9 HEIGHT REDUCTION THERAPY

1.9.1 High-dose sex steroid therapy in girls

Oestrogens cause fusion of the growth plate in normal pubertal development. Observations of children with precocious puberty closing their growth plates early due to premature sex hormone production, led to the development of sex steroid therapies to reduce growth in tall children in the 1950s (Goldzieher 1956).

It has been demonstrated that use of high-dose oestradiol accelerates skeletal maturation which causes premature fusion and a reduced adult height (Nilsson et al. 2014; Weise et al. 2001). When oestrogen therapy was first used in tall girls in the 1950s and 1960s, the synthetic ethinyl oestradiol (EE) was usually administered in daily doses of 500 μg. The dosing was gradually decreased until it was shown that 100 μg of EE daily was sufficient for the desired effect (Drop et al.1998; Bartsch et al. 1988; Joss et al. 1994). An addition of a daily dose of 5-10 mg medroxy progesterone acetate (MPA) was used in most cases for approximately 7-10 days at the end of each cycle to induce a monthly bleeding (Drop et al. 1998). Ethinyl oestradiol is the most commonly administered oestrogen compound for reduction of adult height and is also used in combined oral contraceptives. Other oestrogen compounds have been used for height reduction, such as conjugated oestrogens, oestradiol esters and in the early days diethylstilbestrol (Drop et al. 1998). In 1971, Herbst et al. reported an increased risk of vaginal cancer in girls who had been exposed in utero to diethylstilbestrol and in 1997 the drug was finally taken of the market (Herbst et al. 1971; Wettenhall et al. 1975; Laronda et al. 2012).

1.9.1.1 Efficacy of sex steroid therapy in tall girls

When evaluating the efficacy of the treatment, the reduction in growth is estimated based on the predicted final height before start of the treatment. Based on which of the different prediction methods are used (section 1.7.2), these estimations vary. Hence, growth reduction is often reported as an interval between these values. Drop et al. reported 1.1 to 2.4 cm reductions in adult height compared to prediction in high-dose oestrogen treated girls depending on which method was applied to predict adult height (Drop et al. 1998). In another study of 14 high-dose oestrogen treated girls, growth reductions between 2.3 and 6.5 cm were reported (Sorgo et al. 1984). In this study, a small untreated comparison group was included. In the comparison group, predicted heights exceeded final heights with 0.2 to 3.4 cm. Deducting these numbers from the results in the treated group gave a significant result only when using the Bayley-Pinneau method for prediction. The treatment effect was significantly associated with chronologic age and bone age at start of therapy as well as the duration of treatment. De Waal et al. also found a linear relationship between bone age at start of treatment and degree of effect (de Waal et al. 1996). Treatment needed to be started before 14 years of age to have any effect at all. The mean growth reduction in the 159 treated women varied from 1.7 to 4.2 cm depending on prediction method. Venn et al. studied the effect of oestrogen treatment in 279 tall girls and found that their adult heights were reduced by 2.5 cm on average and that the effect decreased by one cm per year of delay in treatment start (Venn et al. 2008).

1.9.1.2 Safety of sex steroid therapy in tall girls

Reported short-term side effects of high-dose oestrogen treatment include acne, weight gain, nausea and headache (de Waal et al. 1995; Binder et al. 1997; Radivojevic et al. 2006; Weimann et al. 1998). With regards to long-term side effects, infertility in women treated with high-dose oestrogens for tall stature has been reported (Venn et al. 2004; Hendriks et al.

2011). The treated women had decreased fecundity, were more likely to have used fertility drugs and had more advanced aging of their ovaries compared to those untreated. An association between oestrogen therapies and thrombosis has been shown in users of combined hormonal contraceptives (Bergendal et al. 2014). An alteration of the coagulation parameters was reported in women previously treated with high-dose oestrogens for tall stature but an increased risk of thrombosis has not been demonstrated in this patient group (Rask et al. 2008). Another concern for tall women previously treated with high-dose oestrogens is a possible linkage with cancer. Studies are lacking but women using oral contraceptives and hormone replacement therapy have been studied with regards to any association with cancer. Breast cancer has been linked to these treatments in some studies but not in others (Jernström et al. 2005; Kahlenborn et al. 2006; Predná et al. 2015). With regards to ovarian cancer on the other hand, contraceptives have been shown to have protective effects (Jatoi et al. 2015; Faber et al. 2013). A demonstrated role for ER-β in the development of malignant melanoma suggests that oestrogen treatment could potentially affect the risk of such cancer (de Giorgi et al. 2011). An association between oral contraceptives or hormone replacement therapy with malignant melanoma has not been found however (Gandini et al. 2011).

Pyett et al. performed a study of long-term satisfaction in 396 adolescent women treated with sex steroids for tall stature. A control group of 448 untreated women were included. About 99% of untreated women were happy that they had not received treatment, regardless of their final heights. Forty-two percent of treated women regretted their decisions to get treatment. Their reasons were negative experiences related to the assessment or treatment, short- and long-term side effects or not being involved in the decision to start treatment (Pyett et al. 2005).

1.9.2 High-dose sex steroids in boys

Boys have also been treated with high-dose sex steroids to reduce adult height and the testosterone compounds used were generally long-acting esters such as testosterone propionate, enanthate, and decanoate (Drop et al. 1998). Testosterone doses of 250-500 mg were usually administered through intramuscular injections every second week and the treatment duration was typically 1.5 years (Reinehr et al. 2011; Drop et al. 1998).

1.9.2.1 Efficacy of sex steroid therapy in tall boys

There are a number of studies evaluating the effect of testosterone treatment in tall boys. A final height reduction of 4.4 cm was reported in 33 treated boys (Binder et al. 1997). Others reported a final height reduction of 4.8 cm when using the Bayley and Pinneau tables for height prediction but as low as 1.7 cm with clinical- and 0.5 cm with Tanner-Whitehouse prediction methods (de Waal et al. 1996). Height reductions of approximately seven centimetres, were found in 25 treated tall boys (Brämswig et al. 1981). Marfan patients treated with sex steroids have been reported to have similar treatment effects as constitutionally tall children (Rozendaal et al. 2005).

Reinehr et al. reported that the commonly used testosterone enanthate doses of 500 mg every two weeks could be reduced to half without compromising the efficacy on final height (Reinehr et al. 2011). Other important factors affecting the efficacy were timing of initiating and duration of the treatment. Failure in optimizing these conditions appears in some cases to have led to an effect opposite to the desired. Drop et al. reported that when treatment was started at a bone age of 14 years or later, final height was increased instead of decreased (Drop et al. 1998). Also, in a study where the high-dose testosterone treatment was limited to six months, the authors concluded that final height was not reduced (Bettendorf et al. 1997). Brämswig et al. on the other hand compared short-term (six months) with long-term (14.25 months) therapies and found them equally effective (Brämswig et al. 1988).

Van den Bosch et al reported that an addition of a low dose of EE (50 µg daily) in the beginning of the testosterone therapy in tall boys caused an instant decrease in height velocity (van den Bosch et al. 1982). Decker et al, on the other hand, found no additional effect of EE in this combination (Decker et al. 2002).

1.9.2.2 Safety of sex steroid therapy in tall boys

Reported short-term side effects of high-dose sex steroid therapy in boys include acne, weight gain, gynecomastia and aggressiveness (de Waal et al. 1995; Binder et al. 1997).

Infertility in men after testosterone treatment has not been shown in contrast to high-dose oestrogen treated women. One study reported that 21 years after testosterone treatment, serum testosterone levels were decreased but semen quality was unaffected as well as the chances of becoming a father (Hendriks et al. 2010). Lemcke et al. also found lower testosterone levels in treated men but no significant effects on testicular volumes or semen quality (Lemcke et al. 1996). Others found no effects on testicle volume, sperm quality nor testosterone levels even though FSH levels were increased (de Waal et al. 1995).

1.9.3 Somatostatin

Somatostatin inhibits GH release from the pituitary gland and somatostatin analogues have been used to treat tall stature. Some studies found mean growth reductions of 3-4 centimetres (Hindmarsh et al. 1995; Carel et al. 2009) whereas others found no effects (Noordam et al. 2006) Gastrointestinal side effects were commonly reported.

1.9.4 Bromocriptine

Bromocriptine is a dopamine agonist that could potentially reduce growth in tall children. Many studies where published in the 1980s with regards to their efficacy (Brion et al. 1985; Evain-Brion et al. 1984; Schoenle et al. 1987; Schwarz et al. 1987). Most studies show that at the follow-up after treatment, the new final height predictions are lower than the ones prior to the treatment but data on the effect on final height and safety are insufficient.

1.9.5 Surgical methods

Epiphysiodesis is a surgical method to stop growth by destruction of the epiphyseal growth plates. It was first described by Phemister in 1933 for correcting leg length discrepancy (Phemister, 1933). With an open approach a block of bone was removed from the physis in the longer leg and put back in a rotated position, in which bony bridges formed and disallowed the bone to continue growing. It has been used commonly thereafter on this indication. In 1949, Blount and Clarke described an alternative surgical method to stop bone growth by stapling the distal femoral and proximal tibial epiphyses (Blount et al. 1949). It was reversible in the sense that growth could in principle continue after staples were removed. Later studies have evaluated the procedure and some found it relatively efficient and safe (Raab et al. 2001; Ross et al. 1997) while others found it unreliable (Brockway et al. 1954).

Since Phemister, the epiphysiodesis has been developed further in a less invasive direction with the hope to minimize the amount of days spent in hospital, scarring and other complications. A percutaneous approach was developed in the 1980s with drilling into the growth plates under image intensifier guidance (Bowen et al. 1984; Canale et al. 1986). A piece of a human growth plate removed at percutaneous epiphysiodesis surgery is shown in Figure 9.

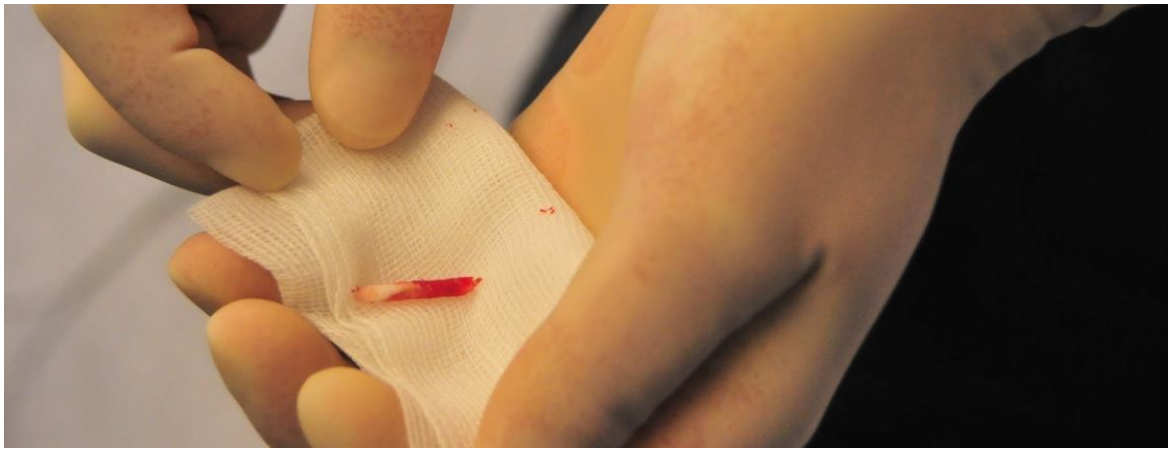

Figure 9. A piece of a human growth plate.

Ross et al. compared the Phemister method, epiphyseal stapling and percutaneous epiphysiodesis in a rabbit model and found them all effective in physeal closure, albeit slower with percutaneous epiphysiodesis likely due to the need for bony bridges to form through a step of fibrous tissue. They suggested this delay might be compensated though by removal of a larger portion of the physis (Ross et al. 1997). Others found the Phemister method and percutaneous epiphysiodesis equally effective but the latter preferred due to less complications (Scott et al. 1996).

Bilateral epiphysiodesis to reduce height in tall adolescents was first described in 1997 (Plaschaert et al. 1997). The Phemister method was used and they reported a height reduction of nine centimetres and no serious side effects in six treated boys. The first report on bilateral percutaneous epiphysiodesis performed to reduce height was published in 2006 and included 17 treated tall boys. The surgery was performed under general anaesthesia. Growth plates of the distal femur, proximal tibia and proximal fibula were located with an image intensifier and curetted after being reached by drilling through one centimetre incisions on both the medial and the lateral sides of the knee. The procedure was found to be safe and reduced the boys final heights with on average 7 cm (range 1.2 -13.8 cm) (Odink et al. 2006).

In recent years, radiofrequency application has been proposed as a new method for epiphysiodesis and has been tested on rabbits (Ghanem et al. 2009; Widmann et al. 2010).

With a surgical approach to reduce height, many of the reported or feared side effects of pharmacological treatments mentioned above can be avoided (Binder et al. 1997; de Waal et al. 1996; Radivojevic et al. 2006; Hendriks et al. 2011). On the downside, surgery always brings a risk of infection and complications associated with the anaesthesia. Also, skeletal deformities are potential side effects.

1.10 HEIGHT-ASSOCIATED HEALTH ASPECTS

1.10.1 Psychosocial aspects of being tall

The most common complaint with tall stature is psychosocial problems. Tall individuals may experience difficulties at school and parents are sometimes concerned of their tall child's ability to find a partner. In an Australian cohort of 650 tall women (approximately one third was previously treated with high-dose sex steroids to reduce their heights), no difference in mental or physical health was found between treated and untreated individuals. However, both these groups had a significantly higher risk of developing major depression compared with population-based studies (Bruinsma et al. 2006).

In a public school in the United States, social outcomes in relation to height were studied in 956 pupils in grade 6-12 in order to establish whether or not there was ground for intervention in extremes of height. They found that there were minimal effects from height on social behaviour and popularity (Sandberg et al. 2004).

There are also studies reporting positive traits associated with tall stature. Higher income in tall individuals has been reported (Rashad 2008). Another study reported that shorter individuals have a lower mood with the exception of those financially disadvantaged. In this group the association between height and mood is reverse (Osika et al. 2008).

A Swedish study of the risk of suicide in association with foetal and childhood growth reported that short adults are more prone to commit suicide and tall adult stature is protective (Mittendorfer-Rutz et al. 2008).

1.10.2 Height and cancer

1.10.2.1 Overview

An association between cancer and height has been explored for many decades in a number of studies. Most cohorts previously studied only included women and the larger studies were mostly meta-analyses. The largest cohort study so far included 1.3 million British women and a relative risk (RR) for total cancer of 1.16 (1.14-1.17) for every 10 cm increase in height was found (Green et al. 2011). Breast cancer risk was increased by 1.17 (1.15-1.19) and melanoma risk by 1.32 (1.24-1.40). Risks of leukaemia, uterine-, ovarian-, CNS-, kidney-, non-Hodgkin-, rectal-, and colon cancer were also increased. A pooled cohort study with more than half a million participants from three European countries including Sweden reported HRs for total cancer risk of 1.07 (95 % CI 1.06–1.09) and 1.04 (95 % CI 1.03–1.06) per 5 cm increase in height in women and men, respectively (Wirén et al. 2014). The largest height-associated risk increase was seen for melanoma and was 1.17 (95 % CI 1.11–1.24) for women and 1.12 (95 % CI 1.08–1.19) for men per 5 cm increase in height. Kabat et al. found a risk increase in total cancer of 13% per 10 cm increase in height in two different cohorts (Kabat et al. 2013; Kabat et al. 2013a). The first included 88,000 Canadian women and the second 144,000 American women.

1.10.2.2 Breast cancer

With regards to specific studies on breast cancer, one large study of approximately 300,000 women found an increase of 26% in ER+ progesterone receptor (PR)+ cancer for the tallest third compared to the shortest (Ritte et al. 2013). Sitting height had a stronger risk association than leg length. A similar association with height was not found for ER-PR- cancer. In a case-control study of women under 45 years of age, the risk of breast cancer was increased by 46 % in the tallest compared to the shortest quartile (Swanson et al. 1996). An approximately doubled risk of breast cancer later in life was found for 15-18 year old girls tall-for-age compared to those short-for-age (Herrinton et al. 2001).

There are also studies with negative results. A large case-control study including 5358 cases and 4555 controls reported no association between height and breast cancer (Zhang et al. 1996). In an Italian case control study no association between height and breast cancer in pre-menopausal women was found (Parazzini et al. 1990). For post-menopausal women, taller individuals had less breast cancer but the association was not statistically significant.

1.10.2.3 Melanoma

In 1993, the association between height and melanoma was studied in a large cohort of 1.3 million individuals. A relative risk of 1.6 for melanoma in the tallest quintile compared to the shortest in both women and men was found (Thune et al. 1993). A more recent cohort study of approximately 99,000 women reported a relative risk of 1.27 (1.05-1.55) for individuals taller than 164 cm compared to those shorter than 160 cm (Kvaskoff et al. 2014). A meta-analysis including 2083 cases and 2782 controls found a relative risk for melanoma of 1.3

(1.1-1.6) in the tallest quartile compared to the shortest. Only women were studied (Olsen et al. 2008).

1.10.3 Height and mortality

Two large meta-analyses published in the last five years including millions of individuals both show a lower all cause- and cardiovascular mortality in taller compared to shorter individuals. The first one includes three million men and women and shows a combined RR (women and men) for all cause-mortality of 1.35 (1.25-1.44) in the shortest compared to the tallest individuals (Paajanen et al. 2010). Cardiovascular mortality was increased by 1.55 (1.37-1.74) in the shortest women and men. The second meta-analysis included 1.1 million men and women and reported a combined hazard ratio (HR) for all-cause mortality of 0.97 (0.96-0.99) for every 6.5 cm increase in height. Hazard ratio for cardiovascular mortality was 0.94 (0.93-0.96) while cancer mortality was increased by a HR of 1.04 (1.03-1.06) for every 6.5 cm increase in height (Emerging Risk Factors Collaboration 2012). Batty et al. studied all-cause- and cancer- mortality in an Australasian population and found that for every 6 cm increase in height, all cause-mortality was decreased by 2 % in women and 3 % in men. Cancer mortality on the other hand was increased by 9 % in women and 5 % in men (Batty et al. 2010). A cohort study of approximately 10,000 British male and female students who were followed for 40 years showed no association between height and all-cause or cancer mortality (Okasha et al. 2000). The authors suggested that the populations in previous studies were rather diverse and that the associations are due to variation in health and nutrition in childhood rather than height itself. In the pooled cohort study of cancer and cancer death described above, HRs for cancer death per 5 cm increase in height of 1.03 (95 % CI 1.01–1.16) in women and 1.03 (95 % CI 1.01–1.05) in men were found (Wirén et al. 2014).

Historical data from the 20th century and earlier show that the lifespan has increased concurrently with height (Crimmins et al. 2006). It has been hypothesized that both increasing heights and decreasing mortality are caused by a decline in infections and inflammations.

There are also studies which report an inverse association between height and mortality. He et al. suggested that the longevity gene Forkhead Box O3 (FOXO3) could explain part of the pathway with which shorter people live longer as they found that it was inversely associated with height (He et al. 2014). They also found that fasting insulin levels were higher in taller people, which is associated with mortality. As for cancer, mortality is also reported to be decreased with a lower energy intake (Willcox et al. 2004). This could potentially mediate a decreased mortality in shorter people given that they have a lower caloric intake than tall people.

2 AIM OF THESIS

The overall aim of this thesis was to study short- and long-term effects of height reduction therapies and how tall stature associates with morbidity and mortality. More specific goals were to study:

1. Tumour risk in women previously treated with high-dose oestrogens for tall stature
2. Efficacy and safety of epiphysiodesis as a surgical method to reduce height in extremely tall adolescents
3. Cancer and cause-specific mortality in association with height in the Swedish population

3 SUBJECTS AND METHODS

3.1 STUDY DESIGN

3.1.1 Research design in paper I

In this cohort study we investigated any risks of tumours associated with high-dose oestrogen therapy for predicted extreme tall stature. The treated women and the untreated controls had all been assessed for tall stature as adolescents. All women were followed up for any event of a malignant tumour and certain precancerous tumours as reported in the Swedish Cancer Register, the Cause of Death Register and in questionnaires. Gynaecological tumours, breast cancer and melanoma were analysed specifically since they have previously been associated with oestrogen exposure.

3.1.2 Research design in paper II

In this clinical study we evaluated the efficacy and safety of bilateral percutaneous epiphysiodesis performed in extremely tall adolescents to reduce their final heights. Patients included in this report were treated between 1998 and 2004 and followed up until they had reached their final heights. The achieved height reduction was measured based on the predicted adult height. Bone deformations and angulations were assessed as well as any other complications associated with the previous surgery.

3.1.3 Research design in paper III

This was a population based cohort study. The first part of the study investigated the association between height and cancer. Overall cancer was covered, as well as site-specific cancers. These included the central nervous system (CNS), colon, rectum, kidney, Hodgkin lymphoma, non-Hodgkin lymphoma, myeloma, leukaemia, malignant melanoma and other skin cancer in both women and men. In addition, breast-, cervix-, endometrium-, and ovarian cancer were studied in women and prostate cancer in men. The association between adult height and cancer was compared with the association between birth length and cancer in an attempt to distinguish between genetic and environmental factors. Catch up-growth was also studied which could theoretically be a proxy for exposure to growth factors in childhood and adolescence.

For the second part, the association between height and mortality was studied. Overall mortality as well as cause-specific mortality was covered. These causes included accidents and violence; circulatory system; congenital anomalies; digestive system; endocrine; nutritional and metabolic; genitourinary system; hematologic (blood and blood forming organs); infections; mental and behavioural disorders; musculoskeletal system and connective tissue; neoplasms; nervous system, eye and ear; perinatal; pregnancy, childbirth and the puerperium; respiratory system; skin and subcutaneous tissue and at last ill-defined symptoms, signs and conditions.

3.2 STUDY SUBJECTS

3.2.1 Study populations in paper I

A total of 390 women accessed for tall stature between 1973 and 1993 in Swedish university hospitals were identified through hospital records. A small group of women (n= 21) refused participation and were therefore excluded. The final cohort included 369 women, with a slightly higher number of untreated compared to treated women (Figure 10). Follow-up started either at start of treatment (treated women) or time of last height assessment (untreated women) and ended on the 31st of December 2010. A total of 220 women also responded to questionnaires concerning health and previous treatment.

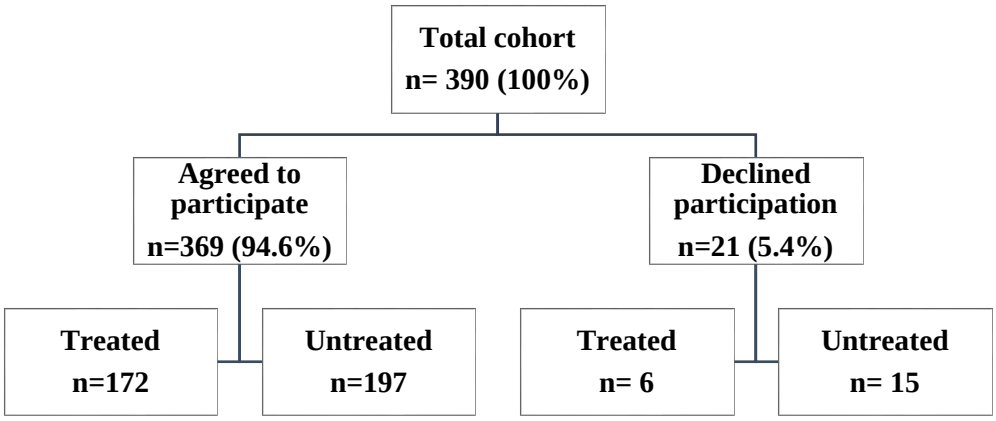

Figure 10. Flow chart of the study cohort I. N= Number of individuals. Percentage of original cohort is shown in parenthesis.

3.2.2 Study populations in paper II

Twenty-one patients (12 girls and 9 boys) were studied after applying inclusion and exclusion criteria as described in Table 3. Informed consents were signed by patients and their parents.

Inclusion criteria:

- Predicted final height ≥ 200 cm in boys and ≥185 cm in girls
- ≥ 8 cm left to grow according to prediction
- Strong patient desire to undergo treatment

Exclusion criteria:

- High sitting height/leg length ratio

Table 3. Inclusion and exclusion criteria for the study cohort in paper II

The majority of patients (n=17) were diagnosed with constitutional tall stature. Two girls and one boy were diagnosed with Marfan syndrome and one boy had Klinefelter syndrome. Patients underwent the surgical procedure between 11 and 16 years of age.

3.2.3 Study populations in paper III

Inclusion and exclusion criteria are listed in Table 4.

Inclusion criteria: • Swedish resident • Born between 1938 and 1991 • Adult height available from registers Exclusion criteria: • Height or death data unreliable • Emigration

Table 4. Inclusion and exclusion criteria for the study cohort in paper III

Due to lacking or unreliable data on death or height (only heights after 18 years of age in women and 20 years in men used), 9930 women and 216,636 men were excluded. The number of individuals excluded due to emigration was 47,528 women and 42,084 men. From an original cohort of 5.8 million individuals, a total of 2,737,661 women and 2,777,828 men were included in our final analysis. They were followed for a total of over 70 million person years. Figure 11 shows the distribution of height data from the different sources.

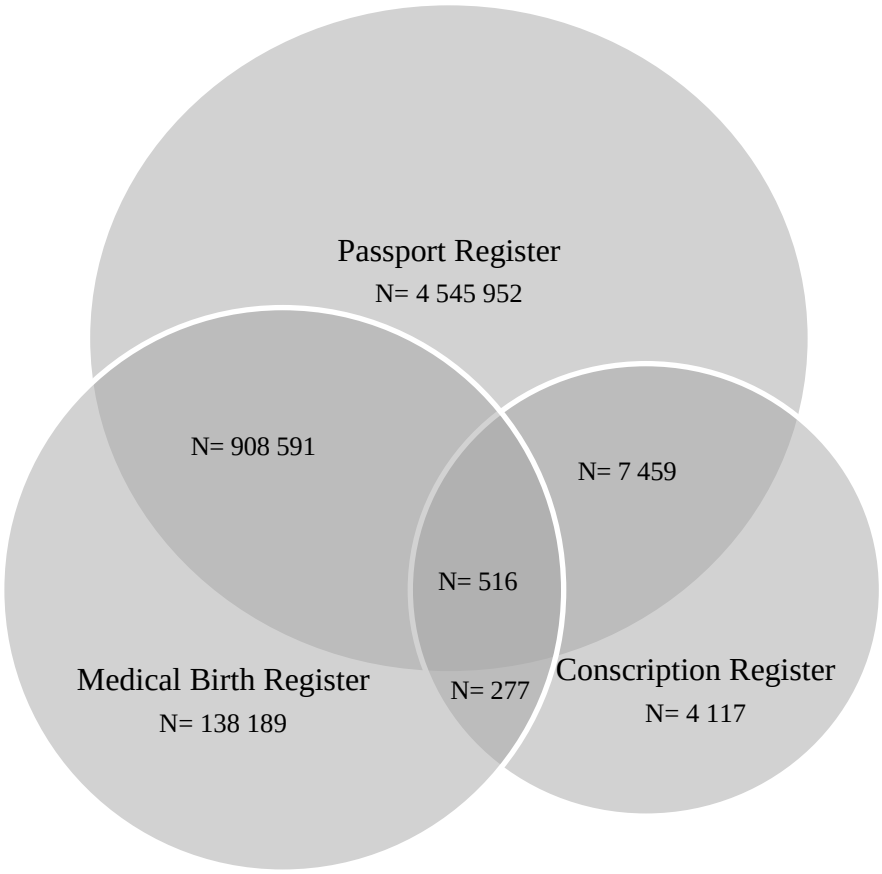

Figure 11. Register contribution of height data. Each circle represents a different register (not to scale). N in each subset indicates the numbers of individuals for whom height data were available.

3.3 DATA SOURCES

3.3.1 National registers

3.3.1.1 Swedish Passport Register

The Swedish Passport Register data is held by the Swedish National Police Agency and was computerized in 1991. All individuals in the Swedish population who had a passport issued from this year onwards, could contribute with height data (paper III). These are either self-reported or measured on site at time of the passport application.

3.3.1.2 Swedish Conscription Register

The Swedish Conscription Register includes information on height, weight, results from physical examinations and cognitive tests at the time of military recruitment. Mainly men but also a small number of women undergo military recruitment and have their heights registered. Enrolment was mandatory for all men except those with severe handicaps and enforced by law in Sweden until July 2010. Military service tests are normally performed at the age of 18. The earliest records from 1969-1997 are held by the National Archives and data from 1983 until present are available from the Swedish Defence Recruitment Agency. These height data were used in paper III.

3.3.1.3 Swedish Medical Birth Register

The Swedish Medical Birth Register includes information about maternal factors, pregnancy and delivery. We were able to retrieve height data from mothers who have given birth (paper I and III). Information about the neonatal period is provided through antenatal, obstetrical, and neonatal records. The register started in 1973 and covers between 97.0-99.5% of all births. The number of births per annum in Sweden has varied over the years from between 86,000 to a bit over 120,000 (www.socialstyrelsen.se/register/halsodataregister/medicinskafodelseregistret).

3.3.1.4 Swedish Cancer Register

The Swedish Cancer Register was used to study cancer incidence in the two different cohorts in paper I and III. The register started in 1958 with the purpose of recording the annual incidence of cancer in the population and following trends over time. The reporting of all cases of cancer and some certain precancerous tumours are mandatory by law. Clinical and morphological diagnosis, tumour staging as well as date of diagnosis for the primary tumour are registered. Information about metastases is available when the primary tumour location is unknown. Every year about 60,000 cancer cases are reported in the Swedish population which consists of approximately 9.5 million people. According to a study, 96.3 % of tumours are reported (Barlow et al. 2009). Out of these tumours, 99% are verified morphologically (www.socialstyrelsen.se/register/halsodataregister/cancerregistret).

3.3.1.5 Swedish Cause of Death Register

The Swedish Cause of Death Register records all times and causes of death for Swedish residents except stillbirths with over 99 % coverage. Data on time and cause of death were used for the populations in paper I and III. Deaths occurring outside Sweden are included unless the individual has emigrated. Causes of death are coded according to the international classification of diseases (ICD), revisions 7 through 10. The register is updated annually (http://www.socialstyrelsen.se/register/dodsorsaksregistret).

3.3.1.6 LISA Register

Statistics Sweden supplied socioeconomic data (paper III) from a specific database called longitudinal integration database for health insurance and labour market studies (LISA by Swedish acronym). It holds information on all individuals from 16 years of age since 1990 including employment, income, unemployment benefits, parental leave, illness, studies, pensions, education level and place of residency (www.scb.se).

3.3.2 Medical records

Hospital records in electronic chart systems and local hospital archives were used to retrieve treatment information of the cohorts in paper I and II as well as to follow up the patients in paper II. Records were also used to recruit control groups of boys and girls who had sought medical advice for tall stature (paper I and II).

3.4 EXPOSURES AND OUTCOMES

3.4.1 Paper I

3.4.1.1 Treatment

The prior treatment to reduce final height consisted of EE with daily doses varying between 100 and 1000 µg. Most girls were started on cyclic treatment regimens with 3 weeks of medication followed by one oestradiol free week. Typically, MPA was administered for 5-14 days at the end of the oestradiol cycle at a daily dose of 5 mg.

3.4.1.2 Tumour incidence

All tumours reported to the Swedish Cancer Register and the Swedish Cause of Death Register were analysed including all malignant tumours and certain precancerous tumours such as severe dysplasias and melanoma in situ. Malignant tumours were analysed specifically in a separate analysis. Information on tumour incidence in the population was available from the Swedish National Board of Health and Welfare and used for reference (http://www.socialstyrelsen.se/statistik/statistikdatabas).

3.4.1.3 Potential confounders

As height was considered a potential confounder, the participating women were asked to report their adult height, when filling in the questionnaires. Precise instructions on how to measure height were supplied. Height was also available from the Swedish Medical Birth Register for those women who had given birth. Predicted height was another potential confounder and was retrieved from medical records. In order to establish any differences in socioeconomic status between treated and untreated women that could bias the results, women were asked about level of education and employment in the questionnaires.

3.4.2 Paper II

3.4.2.1 Surgical technique

Bilateral percutaneous epiphysiodesis was performed in the growth plates of the distal femur and proximal tibia and fibula under general anaesthesia to induce growth arrest.

By applying a tourniquet, a bloodless field was created. An X-ray image intensifier was used to ensure proper localization of the delicate structures. After infiltration of local anaesthesia, a 1 cm incision was made at the lateral aspects of the femoral and tibial growth plates where epiphysiodesis was done with an 8 mm drill bit. Today the procedure has been refined to needing only a 5 mm incision and a 4.5 mm drill bit.

The growth plate was then curetted with both straight oval and angulated oval curettes (5-7 mm), as shown in Figure 12. For the fibula a 3 mm straight oval curette was used through the tibial incision with an anterior approach to avoid damage to the peroneal nerve. To ensure formation of bony bridges over the physis and cessation of growth, approximately 25-50% of each growth plate was removed. Thorough removal of curetted tissue from the subcutaneous spaces is essential in order to avoid formation of extraosseous tissue.

When the epiphysiodesis was completed, the surgical incisions were closed with intracutaneous sutures and tissue glue. Total operation time was approximately one to one and a half hours (30-45 minutes per leg). The operation time has since then been reduced to no more than one hour (30 minutes per leg). Postoperatively, patients were allowed full weight bearing with crutches, but were supposed to avoid physical exercise for a period of four weeks.

Operation images from epiphysiodesis

A **B**

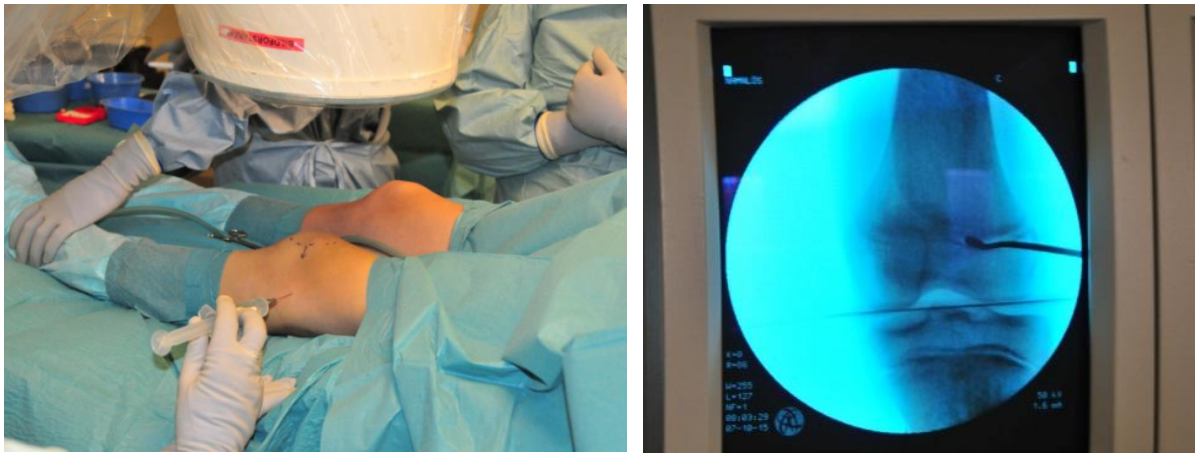

Figure 12. Femur. The femoral growth plate was reached in a position parallel with the centre of the patella. Local anaesthesia was injected adjacent to the incision (A). The angulated curette is visible on the X-ray image (B).

A **B**

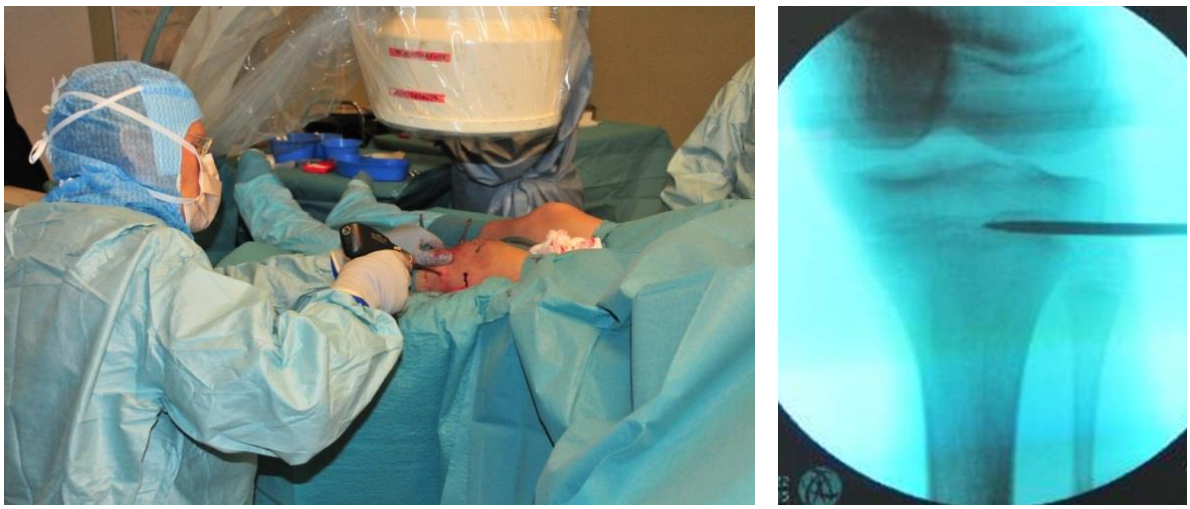

Figure 13. Tibia/fibula. To reach the tibial growth plate, the incision is made slightly anterior of the fibula and the drill is therefore pointing in a slightly dorsal direction.

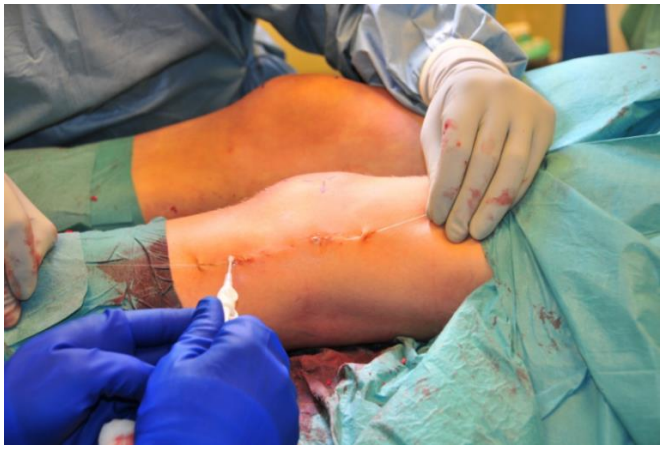

Figure 14. Closing. After the intracutaneous sutures, tissue glue was applied as the very last step of the surgery.

3.4.2.2 Efficacy

Treated patients were followed up according to a specific protocol (Figure 15). The effect of the surgery was measured as the reduction of remaining growth after surgery compared to the predicted. Final height predictions were made independently by two blinded experts according to the Bayley and Pinneau tables (Bayley et al. 1952). These were based on the assessment of bone age applying the Greulich-Pyle method (Pyle et al. 1971).

Visit **Day/Month, Year**		**……/…** **20…**	**…/……** **20…**	**……/…** **20…**	**……/…** **20…**	**/** **20…**	**……/……** **20...**	**…/……** **20…**
Time point in relation to surgery	**Surgery** **…../…..** **20….**	**12 mth** **…../…..** **20….**	**24 mth** **…../…..** **20….**	**36 mth** **…../…..** **20….**	**48 mth** **…../…..** **20….**	**60 mth** **…../…..** **20….**	**…../…..** **20….**	**Final height** **…../…..** **20…..**
Height	….cm	….cm	….cm	….cm	….cm	….cm		….cm
Sitting height	….cm	….cm	….cm	….cm	….cm	….cm		….cm
Arm span	….cm	….cm	….cm	….cm	….cm	….cm		….cm
Weight	….kg	….kg	….kg	….kg	….kg	….kg		….kg
Puberty **Tanner stage**	B/G…. Ph….							
Hand X-ray (< 3 months preop) Till LS*	Done ../..20…							
X-ray of both legs -Hip-knee-ankle angle? -Femur & tibiae length? (<3 mth preop, 1 yr postop and at final height) To LS*	Done ../… 20…	Done ../… 20…						Done ../.. 20..

Figure 15. Study protocol. Used in the follow-up of each patient treated with bilateral percutaneous epiphysiodesis.

3.4.2.3 Validation of final height predictions

We recruited 17 untreated patients (12 girls and 5 boys) who had also sought medical attention during the same time period as the treated patients. They had all been diagnosed with constitutional tall stature and had X-rays taken to determine their bone age. Final heights were measured at our clinic, most of them in the evenings whereas the treated patients were usually measured in the morning. In order to adjust for the known height loss during the day, we quantified any such height increment by measuring 12 healthy young adults twice daily.

3.4.2.4 Safety

Safety was evaluated in terms of any complications during surgery such as bleedings and immediately after including postoperative pain and infections. Long-term effects including hip-knee-ankle angulations, leg length discrepancies and disproportions were also evaluated with auxological measurements as well as radiology.

3.4.3 Paper III

3.4.3.1 Definitions of height and growth

Adult height:

- Height appearing most frequently in the three registers combined:
  - Medical Birth Register
  - Conscription Register
  - Passport Register
- The highest of two or more equally frequent heights was chosen
- Excluded (unreliable) heights:
  - Equally frequent heights differing more than 5 cm when no single most frequent height was present
  - < 100 cm in both genders
  - > 225 cm for women and > 240 cm for men
  - Before age 20 years for men and 18 years for women

Birth length:

- Length in the Medical Birth Register
- Excluded lengths:
  - Before week 37 or after week 42
  - < 30 cm or > 60 cm

Catch up growth:

- An increase in height of more than 2 SD from birth length to adult height

3.4.3.2 Cancer incidence and mortality

The study cohort was followed up in the Swedish Cancer Register and the Swedish Cause of Death Register from 20 years of age until death, emigration or the end of the study in 2011. Any non-malignant tumours were excluded and only the primary cancer and primary cause of death were studied.

3.4.3.3 Potential confounders

Socioeconomic factors such as education and income were considered possible confounders and were adjusted for. Smoking was also considered a possible confounder. In order to test this hypothesis, a sub analysis was performed in a group of women for which data on smoking were available from the Medical Birth Register.

Women were asked when registering at a maternity clinic in early pregnancy about their smoking habits currently and three months prior. Their maximal smoking (at either of these times) was counted and they were divided into non-smokers, moderate smokers (1-9 cigarettes/day) and heavy smokers (≥10 cigarettes /day).

3.5 DATA PROCESSING AND STATISTICS

3.5.1 Data linkage

Data was linked between all the different registers as well as hospital records by using the unique personal identity number held by each Swedish resident (Ludvigsson et al. 2009).

3.5.2 Statistics

Analyses were carried out using Microsoft Excel (paper II) and SAS® version 9.3 and 9.4, SAS Institute, Cary, NC, USA (paper I and III). P-values < 0.05 were considered statistically significant.

3.5.2.1 Paper I

To estimate tumour risks associated with oestrogen exposure in adolescence, logistic regression was performed. Adjustments were made for adult height and predicted height. Summary statistics were presented as medians with interquartile ranges (IQRs).

Odds Ratios (ORs) with 95 % Confidence Intervals were computed to assess associations of risks between treatment and development of specific tumours. For outcomes with fewer than five events, the exact method was used. Standardized incidence ratios (SIR) were used to compare the treated group with the general population. SIR is the sum of observed cases divided by the sum of expected cases. The latter were calculated as the number of women under observation multiplied by the population rate which was retrieved from a national database of cancer incidence in Sweden (www.socialstyrelsen.se/statistik/statistikdatabas).

3.5.2.2 Paper II

Student's t-test or Wilcoxon Signed Rank test was used to analyse the effects of the treatment. Pearson's correlation was used to assess the relationship between pairs of variables. Results are presented as means +/- SEM.

3.5.2.3 Paper III

Standard multiple Cox Regression was used and stratifications were made by birth year. We adjusted for education, income and smoking. The time scale was age and started at 20 years. The independent variable (survival time) used was time to specific cancer or time to death from the specified cause. Patients were censored at death in the cancer analysis and death from other than the studied cause in the mortality analysis, emigration, or end of study.

Risk estimates were presented as Hazard Ratios with 95% Confidence Intervals for women and men separately.

3.6 ETHICAL CONSIDERATIONS

All study protocols were approved by the Regional Ethics Board at Karolinska Institutet in Stockholm.

The study subjects in paper I were sent written information about the study along with the questionnaires and an option of 'opt out' (Hultman et al. 2009) whereby they could decline participation. Those opting out were excluded from both the questionnaire and from the register data collection.

For the study in paper II all patients and their parents signed informed consents for participation in the study. For this study it was important to carefully weigh the benefits against the risks since the adolescents treated were healthy. The procedure itself, however, has been used within the field of paediatric orthopaedic surgery for many decades to treat leg length discrepancy and is regarded safe.

It was impossible to inform all 5.5 million study subjects in paper III. All register data were however first anonymized by the National Board of Health and Welfare. Furthermore, our results are aggregated data in which it should be impossible to identify any individuals.

We believe that the integrity of all study subjects has been honoured and preserved.

4 RESULTS

4.1 PAPER I

4.1.1 Baseline characteristics

The treated group included 172 women and the untreated group included 197 women previously assessed for tall stature at an average age of 13 years. The average heights at inclusion were 176 cm in the treated and 175 cm in the untreated group whereas the predicted adult heights were 184 cm in the treated and 181 cm in the untreated group. The therapy was on average initiated at 13.2 years of age and went on for 1.2 years. Medan daily dose was 500 µg of EE and most girls were given 5 mg of MPA at the end of each cycle. At adult age, both groups had reached median heights of 181 cm. The proportions of women with a higher education and full time employment, respectively, were approximately 70 % for both categories in treated as well as untreated women. For more details, view paper I, table 1.

4.1.2 Cancer risk

4.1.2.1 Treated vs untreated patients

Of the 369 individuals who agreed to participate, 27 (16 treated and 11 untreated) developed tumours during the follow-up period. Fourteen women (10 treated and 4 untreated) developed malignant tumours. Median age at tumour diagnosis was 35.0 years (28.7-42.2) in the treated and 34.1 years (30.2-41.0) in the untreated group. The numbers of affected individuals in the two different groups and odds ratios (ORs) for the cancer risk are presented in detail in paper I, table 4. The OR for any tumour (malignant or non-malignant), was 1.7 (0.8-3.8). The OR for breast tumours (all malignant) were 2.3 (0.4-12.8) and for gynaecological tumours 0.8 (0.2-2.6). The OR for any melanoma was 6.1 (1.04-∞). Odds ratios were 3.0 (0.9-9.7) for any malignant tumours, 2.3 (0.2-25.6) for malignant gynaecological tumours and 2.8 (0.3-∞) for malignant melanoma.

To summarize, risks were higher in treated patients for all types of tumours except non-malignant gynaecological tumours but these differences did only reach statistical significant for melanoma (OR 6.1).

4.1.2.2 SIR

The risks of developing cancer compared to expected based on data from the general population were calculated as standardized incidence ratios (SIRs) with 95% confidence intervals in parenthesis. For the treated group, the SIR was 2.27 (1.09-4.17) for any cancers which was statistically significant. For specific cancer types SIRs were not statistically significant. For breast cancer it was 2.84 (0.76-7.28), for gynaecological cancer 2.94 (0.33-10.62), and for malignant melanoma 3.42 (0.38-12.36).

4.1.3 Satisfaction with the treatment

Seventy-six patients (74%) reported satisfaction with the previous treatment (because of achieved effect). However, 8 patients (8%) were unsatisfied (because of lack of effect, associated side effects, fear of long-term side-effects or no longer viewing tall stature as a problem). Nineteen patients (18%) did not know or did not answer.

4.2 PAPER II

4.2.1 Baseline characteristics

Treated girls were predicted to reach mean final heights of 190.5 cm and boys 205.5 cm. Girls were operated at an average age of 13.1 years with a mean height of 178.7 cm and a delay in bone age of 0.8 years. Boys were treated at 14.1 years with a mean height of 187.7 cm and a delay in bone age of 0.3 years (for further details, view paper II, table 3).

4.2.2 Treatment effect

Remaining growth after surgery was reduced by approximately one third of predicted in both genders (Table 5). The mean increase in height after surgery was 7.7 cm in girls and 11.4 cm in boys, respectively, and growth occurred mainly in the upper body segment (Figure 16). All treated boys and girls grew up to just over one centimetre in the legs after surgery, except one boy who grew 3.3 cm in the legs. This particular individual was diagnosed with Marfan syndrome and an X-ray one year postoperatively showed that his distal tibial growth plates were still open. These growth plates are not affected with this procedure. The achieved final height reduction was negatively correlated with the bone age at time of surgery (paper II, figure 3).

The control group used to validate the final height predictions was similar to the treated group in terms of height, chronological- and bone age at time of initial assessment. Final height predictions were approximately five to six centimetres lower in the control group (184.0 ± 1.0 cm and 200.7 ± 2.2 cm in girls and boys, respectively). In this group, girls were overpredicted by a mean of 0.2±0.6 cm and boys overpredicted by a mean of 1.3±1.8 cm. After also taking into consideration the hourly loss in height that normally takes place during the day which we quantified (since the control patients were measured in the evenings), girls were overpredicted by 0.1 cm and boys by 0.5 cm. Given the small size of the error, we decided not to correct for this in the final analysis.

	PFH (cm)	FH (cm)	Height reduction (cm)
Girls	190.5 (186.0-193.5)	186.4 (182.8-189.8)	4.1 (1.5-10.0)***
Boys	205.5 (196. 0-121.8)	199.1 (191.7-208.5)	6.4 (0.3-10.7)***

Table 5. Predicted, final and reduced height. PFH= predicted final height at surgery. FH= final height. Height reduction = PFH - FH. Values are presented as means (range). *** p<0.001 vs PFH at surgery.

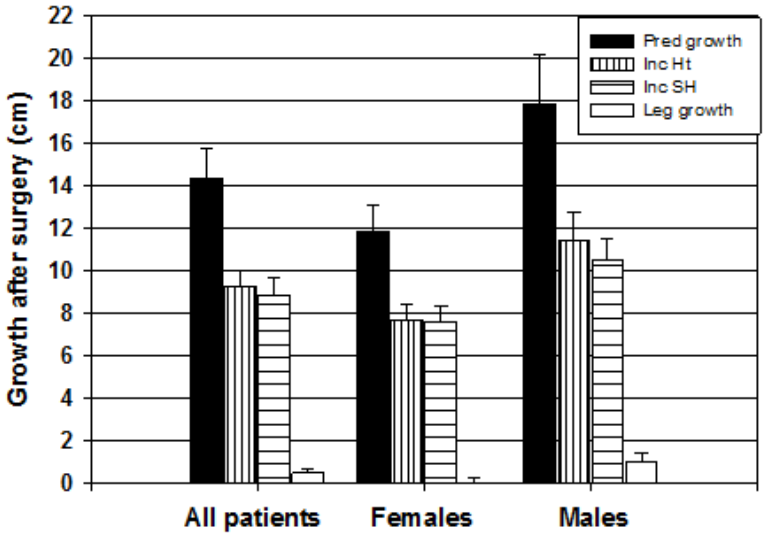

Figure 16. Growth reduction. Pred growth= predicted growth. Inc Ht= increase in height. Inc SH= increase in sitting height. Leg growth= increase in leg length from time of surgery.

4.2.3 Safety of the treatment

Nine patients had postoperative pain which required oral analgesics for up to two weeks. One patient had a postoperative superficial cutaneous infection that did not need antibiotic treatment. The operation did not cause any increased leg length discrepancies in the patients. Hip-Knee-Ankle angle was increased by 0.5-5.0 degrees in seven patients and decreased by 0.5-5.0 in ten patients. With regards to body proportions, all operated patients except three had a relative sitting height below the mean for age at time of surgery. At final height, relative sitting height was still below the mean in girls and for boys just slightly above the mean (paper II, figure 4).

4.3 PAPER III

4.3.1 Baseline characteristics

The 2.7 million women and 2.8 million men were divided into five different birth cohorts. Their mean heights increased by 1.8 cm in women and 2.5 cm in men on average from the first to the last birth cohort (Table 6).

Birth year		**1938-1950**	**1951-1960**	**1961-1970**	**1971-1980**	**1981-1991**
Number of study subjects	Women	661,948	528,189	584,665	530,132	432,727
	Men	661,211	534,443	599,351	540,446	442,377
Mean height (SD)	Women	165.07 (5.77)	165.80 (6.11)	166.45 (6.29)	166.68 (6.38)	166.86 (6.31)
	Men	178.41 (6.42)	179.54 (6.73)	180.23 (6.85)	180.49 (6.85)	180.90 (6.84)

Table 6. Mean height per birth cohort. Baseline adult height for women and men (mean and SD) for five different birth cohorts.

4.3.2 Cancer risk

The Crude HR for any cancer in women was 1.19 (1.18, 1.20) per 10 cm increase in height (paper III, figure 1). For men, the corresponding HR for any cancer was 1.11 (1.10, 1.12). HR for breast cancer in women was 1.23 (1.21, 1.24) per 10 cm. For all cancer sites studied except myeloma in women, risks were significantly associated with increasing height. Melanoma had the strongest association in both genders, with HR 1.39 (1.35, 1.43) in women and 1.34 (1. 30, 1.38) in men per 10 cm increase in height, followed by Hodgkin lymphoma and other skin cancer.

4.3.3 Mortality

For women, crude HR for overall mortality was 0.98 (0.97 - 0.99) and for men 0.91 (0.90 - 0.92) per 10 cm increase in height (paper III, figure 2). HR for cancer mortality was 1.15 (1.13 - 1.17) in women and 1.05 (1.03 - 1.07) in men per 10 cm. A number of death causes were increased in shorter individuals including cardiovascular disease where HR was 0.81 (0.78 - 0.84) in women and 0.89 (0.87 - 0.91) in men per 10 cm increase in height. Mortality associated with mental disease was decreased especially in women, with HR 0.75 (0.65 - 0.86) per 10 cm height increase.

4.3.4 Birth length and catch-up growth

When comparing the height- and cancer associations between birth- and adult height, respectively, no clear differences were found (paper III, supplementary figure 1). When adjusted for adult height, isolated catch-up growth was not associated with cancer (Figure 17).

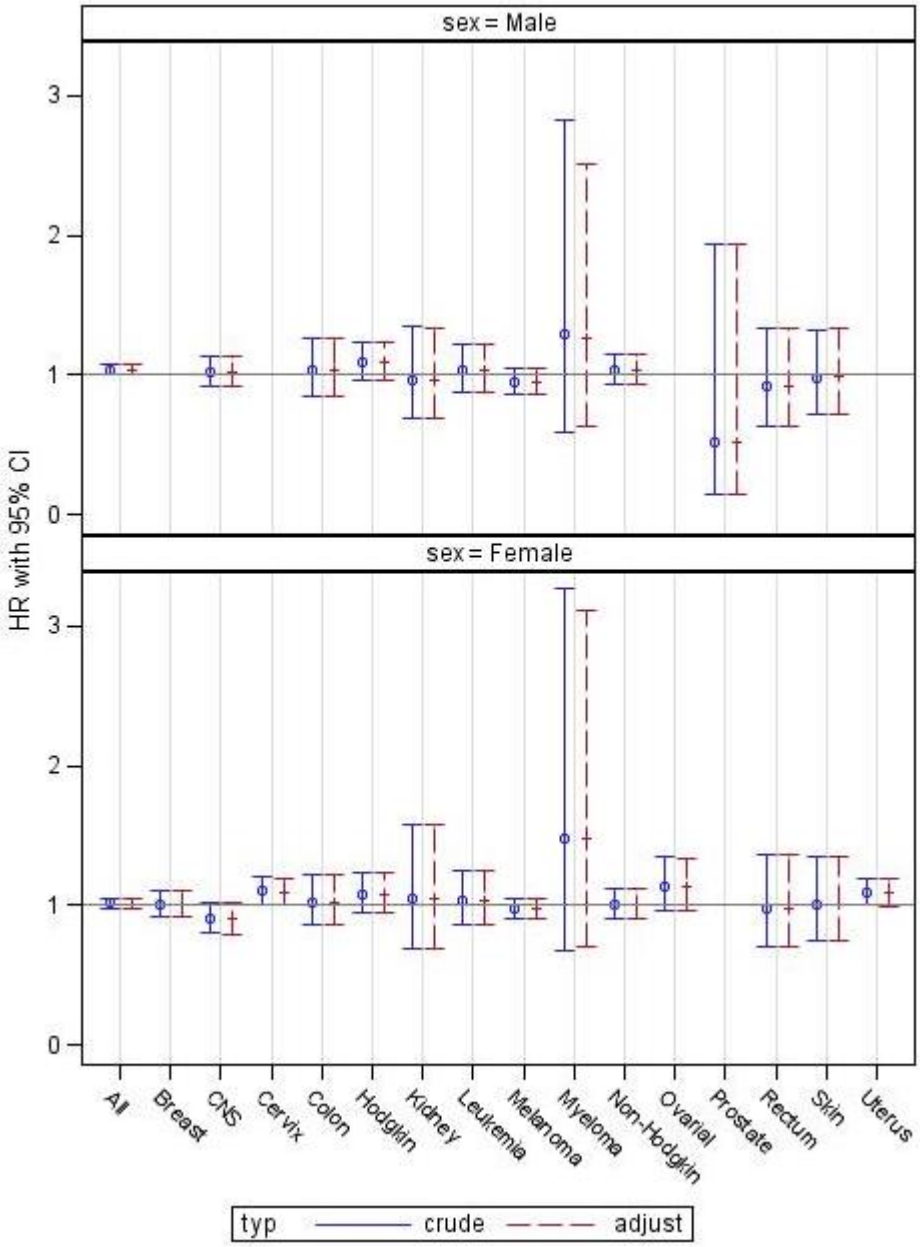

Figure 17. Catch-up growth and cancer risk. Hazard ratios (HRs) per 10 cm height increase and 95% confidence intervals (CIs) for cancer in those with a catch-up growth of 2 SDs or more from birth to adult height compared to those without catch-up growth. Blue lines represent crude values and red lines represent estimates adjusted for socioeconomic factors. All estimates are adjusted for adult height.

Overall mortality appeared to be more strongly negatively associated with adult height than birth length, but any differences could not be confirmed statistically (se paper III, supplementary figure 2).

4.3.5 Socioeconomic status and smoking

Socioeconomic status including highest education and highest income did not significantly affect the risk estimates of mortality and cancer (Table 7).

Cancer site	Sex	N	R	Crude HR	Adjusted HR
All	Women	152481	2.12	1.19 (1.18, 1.20)	1.18 (1.17, 1.19)
	Men	125818	1.71	1.11 (1.10, 1.12)	1.11 (1.10, 1.12)
Breast	Women	60498	0.83	1.23 (1.21, 1.24)	1.20 (1.18, 1.22)
Cervix	Women	7241	0.10	1.11 (1.07, 1.16)	1.11 (1.07, 1.16)
CNS	Women	7182	0.10	1.08 (1.04, 1.12)	1.08 (1.04, 1.12)
	Men	6085	0.08	1.12 (1.08, 1.16)	1.11 (1.07, 1.16)
Colon	Women	7213	0.10	1.19 (1.15, 1.24)	1.21 (1.15, 1.24)
	Men	7268	0.10	1.09 (1.05, 1.13)	1.09 (1.05, 1.13)
Hodgkin	Women	1172	0.02	1.37 (1.25, 1.51)	1.34 (1.22, 1.48)
	Men	1536	0.02	1.30 (1.20, 1.40)	1.28 (1.19,1.38)
Kidney	Women	2337	0.03	1.13 (1.05, 1.21)	1.18 (1.10, 1.27)
	Men	4121	0.06	1.18 (1.13, 1.24)	1.22 (1.16, 1.28)
Leukaemia	Women	2572	0.04	1.21 (1.13, 1.29)	1.21 (1.13, 1.30)
	Men	3561	0.05	1.20 (1.14, 1.27)	1.20 (1.14, 1.27)
Melanoma	Women	12452	0.17	1.39 (1.35, 1.43)	1.32 (1.28, 1.36)
	Men	12452	0.17	1.34 (1.30, 1.38)	1.27 (1.23, 1.31)
Myeloma	Women	12452	0.17	1.39 (1.35, 1.43)	1.32 (1.28, 1.36)
	Men	10080	0.14	1.34 (1.30, 1.38)	1.27 (1.23, 1.31)
Non-Hodgkin	Women	4922	0.07	1.24 (1.18, 1.30)	1.24 (1.18, 1.30)
	Men	4922	0.07	1.16 (1.12, 1.20)	1.16 (1.12,1.20)
Ovarian	Women	7256	0.10	1.21 (1.16, 1.26)	1.20 (1.16,1.25)
Prostate	Men	41674	0.56	1.10 (1.08, 1.11)	1.06 (1.04, 1.07)
Rectal	Women	4284	0.06	1.09 (1.04, 1.15)	1.10 (1.05, 1.16)
	Men	5464	0.07	1.07 (1.03, 1.12)	1.09 (1.04, 1.14)
Skin	Women	3609	0.05	1.32 (1.25, 1.40)	1.29 (1.21, 1.36)
	Men	4527	0.06	1.22 (1.17, 1.28)	1.18 (1.13, 1.24)
Uterine	Women	15893	0.22	1.08 (1.05, 1.11)	1.07 (1.04, 1.10)

Table 7. Comparison between crude and adjusted cancer risks. Associations are presented as hazard ratios (HRs) per 10 cm increase in height. All risk estimates are stratified by age and adjusted HRs are adjusted by socioeconomic factors. CI= confidence interval. Rates indicate the number of cases per 1000 person years.

A sub analysis was performed in a group of women where smoking was adjusted for. Smoking did not have a significant effect on the association between height and cancer in this group (Table 8 and Figure 18).

Cancer site	Crude HR (CI)	Smoke adjusted HR (CI)
Overall	1.19 (1.18-1.20)	1.18 (1.17-1.19)
Breast	1.23 (1.21-1.24)	1.20 (1.18-1.23)
Melanoma	1.39 (1.35-1.43)	1.31 (1.26-1.36)

Table 8. Smoke adjusted height- and cancer association. HR= Hazard ratio. CI= 95 % Confidence Interval.

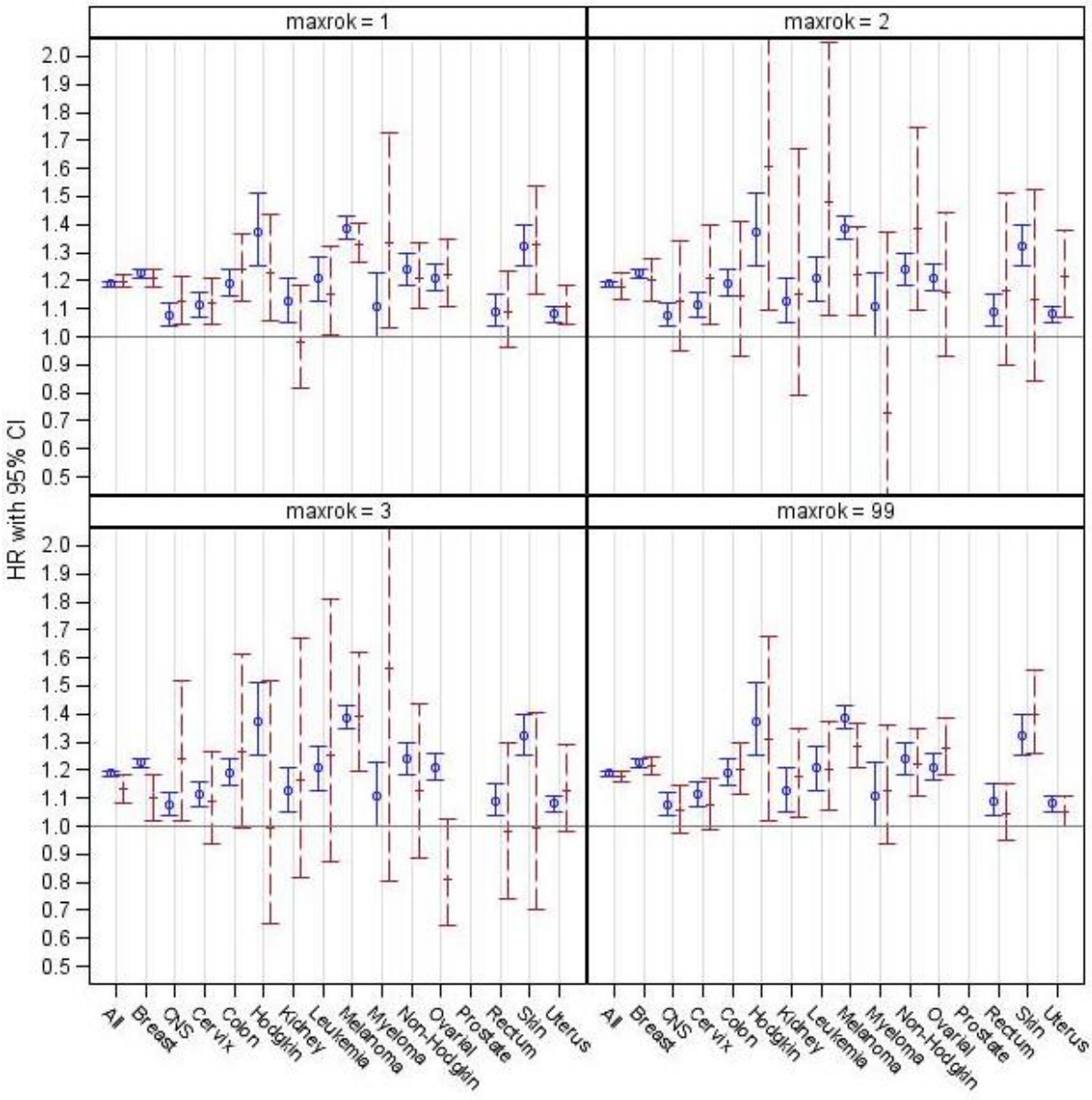

Figure 18. Height-associated cancer risk for different categories of smokers. Red lines represent hazard ratios (HRs) per 10 cm height increase and 95% confidence intervals (CIs) for smokers. Maximal smoking (Maxrok) is explained as follows: 1= non-smoker; 2= light/moderate smoker (1-9 cigarettes/day); 3= heavy smoker (≥10 cigarettes/day); 99= missing information on smoking. Blue lines represent HRs and CIs for the whole cohort independent of smoking habits.

5 DISCUSSION

This thesis provides data on efficacy and safety of two different methods to reduce final height. It shows that high-dose oestrogens administered to tall adolescent girls increases the risk of melanoma later in life. Epiphysiodesis, a new surgical intervention for height reduction, is an efficient and safe method to reduce height in tall girls and boys.

This thesis also contributes to the understanding of how height is associated with health and mortality through a register based cohort study which is larger than any others previously published and includes both women and men. It shows that taller individuals have a higher risk of developing and dying from cancer. Overall mortality is however unaffected by height in women and actually decreased in taller men due to other death causes being negatively associated with height, including cardiovascular disease.

Psychosocial motives drive tall patients to seeking medical attention and almost every week of the year, one or more children visit the paediatric endocrine clinic in Karolinska University Hospital due to concerns of tall stature. High-dose sex steroid treatment for tall stature is not used at Karolinska anymore due to potential long-term effects such as cancer and infertility. The latter has been shown in a number of reports (Hendriks et al. 2011; Venn et al. 2004). Our study of cancer incidence in adulthood after previous high-dose oestrogen treatment to reduce further growth showed that treated girls have a higher risk of melanoma. Overall cancer and breast cancer were also more common in treated girls but these differences were not statistically significant. This may be due to the cohort being relatively small (n=369) and short follow-up time (28 years after treatment) considering cancer incidence increases dramatically with age leading to relatively few cancer cases during follow-up (n=27). To our knowledge there are no previous studies on any association between this treatment and risk of melanoma. In two studies of melanoma risk after oral contraceptives and hormone replacement therapy after menopause, respectively, no increased risks were found (Gandini et al. 2011; Tang et al. 2011). However, a role for ERβ in the development of malignant melanoma has been previously reported (de Giorgi et al. 2011). It is desirable that studies of cancer risk in oestrogen treated tall women are repeated in a larger cohort and even more importantly, with a longer follow-up.

Tall patients presenting in our paediatric endocrine clinic might be offered to undergo epiphysiodesis, given that they have a predicted final height exceeding 3 SD above the mean and a strong desire for intervention. We showed that epiphysiodesis reduces final height with about a third of the remaining predicted growth which in our study corresponded to approximately four centimetres in girls and six and a half centimetres in boys. The effect was affected by the patient's degree of bone maturation. Hence, the earlier the patient was treated, the larger the effect. However, earlier assessment also means a less reliable final height prognosis and therefor the treating physician needs to balance these two opposing factors when timing the surgery. We recommend that a treatment decision is taken before girls have reached a height of 170 cm and boys 185 cm to ensure they have at least 15 centimetres left to grow, which will give a height reduction of at least five centimetres. No short-term side

effects were reported from our patients besides mild to moderate pain and one simple infection postoperatively. In addition to auxological measurements, treatment efficacy and safety were verified radiologically. We have not yet been able to follow these individuals with regards to the long-term safety. There is one previous report of treatment outcome after bilateral percutaneous epiphysiodesis which included only boys (Odink et al. 2006). The height reductions in our male patient group are very much in line with the results in the study by Odink et al.

However, there are important ethical considerations to address before offering treatments to reduce height. What is the long-term value of the treatment? Is it possible that the psychosocial impact of being extremely tall is pronounced only during adolescent years due to peer pressure and reluctance to stand out, factors for which the importance diminishes with age? These individuals are generally healthy adolescents. Few side effects or long-term complications are tolerable under such circumstances. There are no known significant physical problems associated with height per se that could be avoided by reducing further growth potential. We found that in our cohort of women treated with high-dose oestrogens during their adolescence, the majority were happy with their decision 28 years later. Although, we recommend not using this treatment due to the risk of undesired long-term effects mentioned above. Nonetheless, further investigation is needed to assess how mental health is affected by height reducing treatment in the long run.

We tried to get a deeper understanding of the effect of height on a broad perspective on an individual's health. Thanks to the extensive national registers we had access to data on height, cancer, deaths and socioeconomic factors in 5.5 million women and men in the Swedish population. This gave us a unique opportunity to study how height was associated with overall and specific cancer as well as overall and cause-specific mortality in a very large setting. We found that tall individuals have a higher risk of developing cancer overall as well as cancer of the cervix, CNS, colon, kidney, ovary, prostate, rectum, skin, uterus, Hodgkin and Non-Hodgkin lymphoma, myeloma and malignant melanoma. Overall cancer was increased by 1.19 (1.18, 1.20) in women and 1.11 (1.10, 1.12) in men for every 10 cm increase in height. Melanoma was the specific cancer most strongly associated with height (HR 1.39 in women and 1.34 in men) followed by Hodgkin lymphoma and skin cancer. In women we found 20-30 % risk increases for breast-, ovarian cancer, non-Hodgkin lymphoma and leukaemia. Slightly larger associations were generally seen for women than for men but one must keep in mind that a 10 cm increase in height is a larger proportion of a woman's total height than a man's. Also, men and women differ in their hormonal status and other physiological aspects that might affect cancer development. Our results are in line with previous studies on height and cancer (Green et al. 2011; Wirén et al. 2014; Kabat et al. 2013b; Ritte et al. 2013; Olsen et al. 2008). The largest cohort study before ours to our knowledge included 1.3 million women and reported a relative risk of overall cancer per 10 cm increase in height of 1.16 which is very close to our risk estimate of 1.19 (Green et al. 2011). They found increased risks associated with tall stature for many of the same cancer sites as we did, namely: colon, rectum, breast, endometrium, ovary, kidney, CNS, malignant

melanoma, non-Hodgkin lymphoma and leukaemia. For multiple myeloma they found a RR of 1.11, close to our HR of 1.13 and like in our study, this association was not statistically significant.

But what are the mechanisms behind a height-associated increase in cancer risk? One hypothesis that has been discussed in literature is that taller individuals are being exposed to larger quantities of GH and IGF-1 in their childhood and adolescence. Could they act oncogenic (Dunn et al. 1997)? Another is that tall people have a larger number of cells in their bodies which could potentially undergo malignant transformation. Some researchers suggest that taller people have a higher caloric intake which is associated with an increased cancer risk. A modest association was found between energy intake and postmenopausal breast cancer in a cohort study of 29,000 women (Sue et al. 2009). Establishing the mechanisms behind the association between height and cancer risk could potentially facilitate development of different therapies, such as cancer treatment.

For the association between height and mortality, previous studies are inconclusive. Some have found that being tall means a longer life span (Emerging Risk Factors Collaboration 2012; Paajanen et al. 2010), whereas others report that taller individuals live shorter (He et al. 2014; Salaris et al. 2012; Holzenberger et al. 1991). Most studies however found that cancer mortality is positively associated with height (Emerging Risk Factors Collaboration 2012; Batty et al. 2010), and cardiovascular mortality is negatively associated with height (Emerging Risk Factors Collaboration 2012; Paajanen et al. 2010), as was also found in our study. We found that taller men had a decreased overall mortality, HR 0.91 (0.90 - 0.92), whereas overall mortality was not notably affected by height in women, HR 0.98 (0.97 - 0.99).

In summary, the studies in this thesis increase the knowledge of how an individual's health is affected by height per se as well as by different interventions to reduce adult height. This can all contribute to better management of individuals who seek medical attention for tall stature.

6 CONCLUSIONS

- Tall women treated with high-dose oestrogens in adolescence to reduce final height have a higher risk of developing melanoma. Overall tumours and breast tumours were also more common in treated women but these differences were not statistically significant.
- Epiphysiodesis is a safe and efficient surgical method to reduce final height in adolescents with a predicted extreme tall stature. Patients reduced their remaining growth with a third compared to predicted and no serious short-term side effects were reported.
- Height is positively associated with overall cancer and a number of specific cancers, especially malignant melanoma, as well as cancer mortality. Height is negatively associated with overall mortality in men and a number of specific death causes, such as cardiovascular disease, in both women and men and psychiatric disease in women.

7 FUTURE PERSPECTIVES

7.1 FURTHER FOLLOW-UP OF EXISTING TREATMENT METHODS

7.1.1 Long-term follow-up after epiphysiodesis

It is desired to conduct long-term follow-up studies after epiphysiodesis to detect any late complications. Potential long-term side effects could be arthrosis and bone deformations. It is also important to assess satisfaction with the treatment later in life, which could be evaluated with different standardized quality of life-questionnaires.

7.1.2 Tall stature and mental health

We would like to further investigate the association between height and psychiatric disease seen in women to better understand what impact height has on mental health. This could be achieved by studying psychiatric diagnoses in national inpatient- and outpatient health registers.

7.2 DEVELOPMENT OF ALTERNATIVE TREATMENT MODALITIES

7.2.1 Pharmacological treatment

Selective oestrogen receptor modulators (SERMs) are compounds which have different agonistic or antagonistic oestrogen effects in in a tissue-specific manner. They do not exhibit the steroid structure of oestrogens but have affinity to oestrogen receptors. SERMS have been designed to treat breast cancer and osteoporosis (Mirkin 2015). Potentially they could also be used to alter growth by selectively affect oestrogen receptors in bone while limiting side effects in other tissues such as breast and uterus. An example of a SERM is Tamoxifen, which is an ERα antagonist in the breast and an agonist in the uterus and is used to treat breast cancer. It has also been shown to delay bone maturation. Raloxifene, on the other hand, is an oestrogen agonist in both breast and uterine tissue with an agonistic effect on ERβ in the growth plate. Studies on rabbits exposed to Raloxifene showed accelerated growth plate closure without uterus enlargement which was seen in oestrogen treated controls (Nilsson et al. 2003).

7.2.2 Non-invasive growth plate destruction

Growth arrest by destruction of the growth plate, similar to the result of percutaneous epiphysiodesis, could potentially be achieved by minimal- or non-invasive methods. An example of a minimal invasive method studied in animals for the purpose of treating leg length discrepancy is radiofrequency ablation (Ghanem et al. 2009; Widmann et al. 2010). Similar methods could perhaps also be used for growth reduction in tall patients. So far clinical studies are lacking regarding the efficacy and safety of non-invasive methods to induce premature growth plate closure.

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