Human growth patterns

-with focus on pubertal growth and secular changes

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In loving memory of my mother, Lena Holmgren *12/3 1947 - † 14/8 2015

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ABSTRACT

Introduction:
Human growth is a dynamic process, an indicator of health and disease. Previous used growth models have been limited in describing the pubertal growth spurt.

Aim:
The overall aim of this thesis is to increase knowledge regarding human growth. The specific aims were to; explore pubertal growth in detail with new estimates from the QEPS model (Paper I); investigate associations between peak BMI_{SDS} in childhood and subsequent growth (Paper I); evaluate secular changes in adult height for Nordic reference populations (in Sweden including parental heights of study populations) and analyse during which growth phases (foetal/infancy/childhood/puberty) changes occur (Paper III); study changes in growth patterns from birth to adult height in two Swedish population based cohorts born in 1974 and 1990 (Paper IV).

Methods:
The main study material was based on longitudinal growth data (height/weight) from two population based GrowUp Gothenburg growth cohorts (~4000) born around 1974 and 1990. The novel QEPS growth model was used for analysing height and growth patterns. By applying four mathematical functions, QEPS describes the individual height gain: Quadratic (ongoing from before birth to adult height), Exponential (rapid gain during foetal life/infancy), Puberty (adding the specific pubertal growth), Stop (ending gain in height to adult height). During puberty, growth can be separated to a specific pubertal function (P) and the QES-function. The Nordic study analysed height data from present and past growth references used in Denmark, Finland, Norway, and from four Swedish growth studies, comparing height at different ages up to adult height; in Sweden including parental height.

Results and conclusions:
Paper I: New estimates from QEPS model including markers of quality (CI) and SDS for onset, middle and end of puberty showed: the later onset of puberty, the greater the adult height. Pubertal gain due to the specific pubertal P-function was independent of age at onset of puberty; boys had higher total gain during puberty due to P-function growth than to QES-function, reversed for girls. The novel pubertal growth estimates enable a more detailed analyse of pubertal growth than previously possible.

Paper II: Higher childhood BMI_{SDS} was associated with more growth before onset of puberty, earlier onset of pubertal growth, less specific pubertal height gain for both sexes, and unchanged adult height. Childhood BMI_{SDS} was inversely associated with the specific pubertal height gain over the entire BMI-spectrum.

Paper III: The Nordic countries have similar positive secular changes in adult height (females +4-7/males and +5-15mm/decade), mainly due to increased height in childhood, the change was more pronounced in parental heights, i.e. the earlier three-decade period and for males. Earlier pubertal growth was seen in the most recent compared to the oldest reference population in all four countries.

Paper IV: When studying changes in height between the 1974 and 1990 cohorts, a positive change in adult height was found (1990), due to more growth during childhood in both sexes and during puberty in girls. The secular change for the progressively earlier onset of pubertal growth has slowed in girls and levelled off in boys. QEPS model is effective detecting small changes of growth patterns, in cohorts born only 16 years apart.

Overall conclusion:
This thesis shows how novel estimates of pubertal growth from the QEPS growth model make it possible to conduct more detailed analyses of pubertal growth than ever before. Relationships between childhood BMI_{SDS} and pubertal growth are shown, and positive secular changes in growth during the last four decades in the Nordic countries and last seven decades for Sweden are found, together with a more detailed analysis of longitudinal growth patterns in two Swedish growth cohorts.

KEYWORDS: Growth, height, QEPS model, puberty, growth pattern, BMI, secular change, growth phases (infancy/childhood/puberty)

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POPULÄRVETENSKAPLIG SAMMANFATTNING

Tillväxt hos spädbarn, barn och ungdomar är en dynamisk process där tillväxt kan spegla hälsa och vara ett diagnostiskt instrument som kan avslöja sjukdomar och psykosocial problematik. Därför är mätning och uppföljning av längd och vikt en av de viktigaste uppgifterna på barnavårdscentraler och inom elevhälsovård. Avvikande eller misstänkt avvikande tillväxt är en vanlig orsak till att barn och ungdomar remitteras till barn- och ungdoms-medicinska mottagningar. Vid kroniska sjukdomar kan tillväxten påverkas och även utgöra ett mått på behandlingseffekt samt välmående. Därför är kunskap om frisk och avvikande tillväxt viktig för barnläkare.

Den individuella tillväxten beror såväl på genetik, avspeglat i föräldralängder, som på miljömässiga och psykosociala faktorer. Hur samspelet mellan dessa faktorer fungerar, dvs. varför ett barn växer som det gör, är ofullständigt utforskat. Tillväxt kan studeras utifrån olika perspektiv; genetiska, fysiologiska/hormonella, antropologiska/matematiska, sjukdoms-relaterade, psykologiska, sociala och ekonomiska.

Tillväxthastigheten är högst kring barnets födelse, då spädbarnstiden präglas av en snabb, men också snabbt avtagande tillväxthastighet. Det genoms-nittliga spädbarnet växer från 50 till 75-80 cm under det första levnadsåret. Under barndomen sker en långsamt avtagande längdtillväxt fram till puberteten då längdtillväxten ökar igen – pubertetsspurten. Tillväxten har förändrats över tid. De senaste 100-150 åren har slutlängden ökat, vilket beror på att barn har haft en större längdtillväxt som spädbarn och under barndomen i senare generationer. Under 1900 talet har också puberteten kommit allt tidigare, vilket är mest välstuderat och sannolikt mest uttalat hos flickor. Detta kallas sekulära förändringar i tillväxt och pubertetsutveckling. Det finns en stor variation i när pubertetstillväxten sker; mellan kön, mellan länder/populationer och mellan individer.

Matematiska modeller kan både beskriva det tillväxtförlopp ett barn har från födelse till färdigvuxen längd och vara viktiga verktyg för analys och forskning kring tillväxt. Tidigare modeller har varit begränsade i att beskriva individuell tillväxt i allmänhet och pubertetstillväxten i synnerhet. I början av forskningsprojektet, som denna avhandling är en del av, färdigutvecklade

forskningsgruppen en ny tillväxtmodell. Denna kan med fyra matematiska funktioner beskriva individuell tillväxt – QEPS. Modellen återfinns på avhandlingens framsida.

Det övergripande syftet med avhandlingen var att utforska längdtillväxt med fokus på tillväxt under puberteten och sekulära förändringar, samt att studera relationer mellan viktstatus (BMI) i barndomen och fortsatt tillväxt.

De specifika syftena med avhandlingen var att

I. Undersöka och hitta nya mått/variabler för det speciella tillväxtmönster som ses under puberteten med variabler från QEPS-modellen (artikel I). Detta för att bättre kunna beskriva individuell pubertetstillväxt och se hur variationen i pubertetstillväxten ser ut i en population av friska individer.

II. Studera hur body mass index, BMI vikt/längd^2 (kg/m^2) som ett mått för kroppssammansättning/viktstatus i barndomen är relaterat till fortsatt längdtillväxt (artikel II), speciellt om/hur pubertetstillväxten påverkas.

III. Analysera sekulära förändringar i längd för nordiska länder under de senaste 40 åren (i Sverige inklusive föräldralängder hos studiepopulationer – analys av slutlängd under senaste 70 år) och analysera var förändringar i längd under olika tillväxtperioder har skett (artikel III).

IV. Utvärdera förändringar i tillväxtmönster från födelse till slutlängd i två svenska studiegrupper födda 1974 och 1990 (artikel IV).

QEPS-modellen användes som analysmetod i alla artiklar utom den tredje. Modellen beskriver med en kvadratisk pågående funktion kontinuerlig tillväxt från fosterliv till slutlängd (Q), E kommer tidsmässigt först och beskriver foster- och spädbarnsperiodens tillväxt (avtagande exponentiellt). P beskriver pubertetstillväxtens acceleration följt av avmattning och S är en stoppfunktion för slutlängd (stoppar Q). När dessa funktioner adderas (Q+E+P+S) kan individuell tillväxt från nyfödd till slutlängd beskrivas genom att amplituderna (höjderna) och tidsskalorna för funktionerna kan varieras. Ytterligare individuell anpassning fås genom att puberteten kan starta tidigare eller senare än genomsnittet vilket påverkar när slutlängden uppnås.

Två stora studiepopulationer (kohorter), födda 1974 och 1990 ingick i studierna, med mätdata (längd/vikt) från födelse till slutlängd, i genomsnitt 24 längdmätningar per individ. Totalt ca 4000 individer har ingått i analyserna, 1974-kohorten från Göteborgs kommun, 1990-kohorten inkluderade även Härryda, Kungsbacka, Kungälv, Mölndal och Partille. Insamlade mätdata med uppgifter om föräldrarnas slutlängder ingick också. Även för den äldsta svenska kohorten (födda 1956) fanns uppgifter om föräldralängder. För de nordiska studierna jämfördes resultat från dessa länders nuvarande och föregående tillväxtreferenser. För Sverige ingick tre studiegrupper (föregående, nuvarande och kommande tillväxtreferenser).

Avhandlingens resultat blev

Nya mått för pubertetstillväxt från QEPS i den första artikeln visade att modellen på ett mer precist och detaljerat sätt än tidigare kan beskriva olika mått för start, mittdel och slut av pubertetsspurten. Total tillväxt och hur mycket av tillväxten som förklaras av den specifika pubertetskomponenten kan beskrivas och hur länge pubertetsspurten pågår. Vidare sågs att ju senare start av pubertetstillväxt, desto längre blev slutlängden, men samtidigt att individer med tidig pubertetsstart växte mer under puberteten, där skillnaderna i slutlängd beror på att de som var sena i sin pubertet totalt hade flera år extra att växa.

Den andra artikelns resultat var att högre BMI i barndomen var förknippat med mer tillväxt före puberteten (högre Q-funktion), tidigare pubertet och mindre pubertetstillväxt (mindre P-funktion). Det fanns linjära samband mellan både högre BMI (övervikt/fetma) och mindre pubertetstillväxt samt tidigare pubertetsstart för båda könen. P och Q tog ut varandra vad gäller slutlängd, vilket innebar att viktstatus i barndomen (BMI) inte var relaterad till uppnådd längd som vuxen.

Den tredje artikeln visade att populationerna i Norden (Danmark, Finland, Norge och Sverige) alla hade en fortsatt positiv sekulär trend i slutlängd av ungefär samma omfattning, 4-7 mm mer ökad längd per årtionde för kvinnor och 5-15 mm mer för män. Jämförelserna av längder i Sverige där även studiedeltaganas föräldrars slutlängder analyserats visade att trenden var mest uttalad avseende föräldralängder, dvs. under tidigare årtionden (mödrar +11mm, fäder +14mm/årtionde). Ökningen av längder vid födelsen fanns inte

(som i vissa tidigare studier) eller under spädbarnstid, utan den berodde främst på ökad tillväxt under barndomen. Alla fyra länderna hade också en tidigarelagd pubertetsspurt i de senast födda studiegrupperna.

Vid jämförelserna i tillväxtmönster/längd mellan studiegrupperna födda 1974 och 1990 var personerna födda 1990 längre på grund av ökad tillväxt under barndomen för båda könen och under puberteten hos flickor. De färdigvuxna kvinnorna var 6 mm längre och männen 11 mm längre i 1990-populationen. Detta bekräftar en positiv sekulär trend i slutlängd i Sverige och visar att QEPS är effektivt för att analysera relativt små förändringar i tillväxtmönster, i studiegrupper som är födda bara 16 år ifrån varandra. För flickor var pubertetsspurten ca 1 månad tidigare i den senast födda studiegruppen, för pojkar sågs ingen statistiskt säkerställd skillnad.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by Roman numerals (and with short titles mentioned in the order they appear).

I. **Anton Holmgren**, Aimon Niklasson, Lars Gelander, A. Stefan Aronson, Andreas F.M. Nierop and Kerstin Albertsson-Wikland.
Insight into human pubertal growth by applying the QEPS growth model *BMC Pediatrics (2017) 17:107*

II. **Anton Holmgren**, Aimon Niklasson, Andreas F.M. Nierop, Lars Gelander, A. Stefan Aronson, Agneta Sjöberg, Lauren Lissner and Kerstin Albertsson-Wikland.
Pubertal height gain is inversely related to peak BMI in childhood *Pediatric Research 2017:81, 448–454*

III. **Anton Holmgren**, Aimon Niklasson, A. Stefan Aronson, Agneta Sjöberg, Lauren Lissner and Kerstin Albertsson-Wikland. **Nordic populations are still getting taller - secular changes in height from the 20th to 21st century**
Acta Pediatrica 2018, Manuscript under revision

IV. **Anton Holmgren**, Aimon Niklasson, Andreas F.M. Nierop, Lars Gelander, A. Stefan Aronson, Agneta Sjöberg, Lauren Lissner and Kerstin Albertsson-Wikland.
Estimating secular changes in longitudinal growth patterns underlying adult height with the QEPS model: the Grow Up Gothenburg cohorts
Pediatric Research 2018:84, 41–49

APPENDIX:

Andreas F.M. Nierop, Aimon Niklasson, **Anton Holmgren**, Lars Gelander, Sten Rosberg and Kerstin Albertsson-Wikland
Modelling individual longitudinal human growth from fetal to adult life QEPS I.
Journal of Theoretical Biology 2016;406:143–165.

CONTENT

ABBREVIATIONS

AH	Adult Height in cm
AN	Anorexia Nervosa
ANOVA	Analysis of Varians (statistical method)
B1-B5	Breast development in girls (Classification)
BA	Bone age
BMI	Body Mass Index
BMI_{SDS}	Standard deviation score for Body Mass Index
BW	Birth Weight
CHC	Child Healthcare Center
CI	Confidence interval
CNS	Central Nervous System
CrescNet	A computer based screening electronic growth chart system
DICT	Delayed Infancy Childhood Transition
DXA	Dual energy X-ray Absorptiometry
EDC	Endocrine Disrupting Compounds
E-HV	E height velocity (first derivate of E function)
EQP	Initial acronym for QEPS
FSH	Follicle Stimulating Hormone
FTT	Failure To Thrive
GA	Gestational Age
GDP	Growth Domestic Product
G1-G5	Testicular volumes in boys (Classification)
GH	Growth Hormone
GnRH	Gonadotropin-Releasing Hormone
GHRH	Growth Hormone Releasing Hormone
GPF54	Receptor for kisspeptin
GP-GRC	Gothenburg Pediatric Growth Research Center
GWA	Genome Wide Association
$Height_{SDS}$	Height position related to the reference standard deviation score
ICP	Growth with Infancy, Childhood and Puberty functions
ICT	Infancy Childhood Transition
IGF-I (II)	Insulin like Growth Factor I (II)
IOTF	International Obesity Task Force

LGA	Large for Gestational Age
LH	Luteinising Hormone
MBR	Medical Birth Registry
MKRN3	Hypothalamic protein inhibiting pubertal onset
MRI	Magnetic Resonance Imaging
Nw	Normal weight according to BMI_{SDS}
Ob	Obese regarding BMI_{SDS}
Ow	Overweight regarding BMI_{SDS}
PB1	Growth model (Preece-Baines)
PH1-PH5	Pubic hair development (Classification)
PHV	Peak height velocity
QEPS	Acronym for the growth model used (see below)
SDS	Standard Deviation Score
SGA	Small for Gestational Age
SITAR	Growth model (Super-Imposed by Translation and Rotation)
Uw	Underweight regarding BMI_{SDS}
WBC	Well Baby Clinic
WC	Waist circumference
WHO	World Health Organisation
WWII	World War two
W/H^x	Weight in relation to Height (X=1, 2 or 3)

Abbreviations from the QEPS model

AgeP1	age at which 1% of the *P*-function growth is reached
AgeP5	age at which 5% of the *P*-function growth is reached
AgeP50	age at which 50% of the *P*-function growth is reached
AgeP95	age at which 95% of the *P*-function growth is reached
AgeP99	age at which 99% of the *P*-function growth is reached
AgePHV	visually estimated age at peak height velocity
$AgeP_{PHV}$	age at peak height velocity of the *P*-function. $AgeP_{PHV}$ for each individual is reached at 48% of the pubertal growth *P*
$AgeT_{END}$	age at the end of puberty where the HV has decreased to 1 cm/y for function *T'(age)*
$AgeT_{ONSET}$	age at minimum height velocity of the *T*-function at start of the pubertal growth

$AgeT_{PHV}$	age at Peak Height Velocity of the *T*-function
E	negative exponential growth function of age *E(age)* in cm
E_{max}	gain in adult height in cm due to *E*-function growth
$E_{timescale}$	individual time scale ratio; modifying the time scale of the *E*-function growth, and therefore inversely related to the tempo of *E*. The origin is at t_0, the age when length is theoretically zero, $E(t_0)=0$, $Q(t_0)=0$
MathSelect	criterion for assessing the quality of the fitted total individual height function
P	quadratic logistic function describing the pubertal growth spurt *P(age)* in cm
$Pgain_{Px\%-y\%}$	gain in total height in cm due to the pubertal growth of the *P*-function from x% till y% of the *P*-function, so $Pgain_{P5-95}$ is the *Pgain* from *AgeP5* to *AgeP95*.
P_{max}	pubertal gain in adult height in cm due to the *P*-function growth, equal to P_{AUC}
$P_{timescale}$	individual time scale ratio, modifying the time scale of the *P*-function and is therefore inversely related to the tempo of *P*. The origin is at *AgeP50*, the age at which 50% of the individual *P*-function is reached
Q	quadratic growth function of age *Q(age)* in cm
$QESgain_{Px\%-y\%}$	gain in total height in cm due to the pubertal growth of the *QES*-function from x% till y% of the *P*-function, so $QESgain_{P5-95}$ is the *QESgain* from *AgeP5* to *AgeP95*.
QES	*Q+E-S*
QESpubgain	$QESgain_{P5-100} = QES_{max} - QES(AgeP5)$
QEPS-HV	Height velocity of total QEPS (T) curve
Q_{max}	gain in adult height in cm due to *Q*-function growth
S	stop function *S(age)* in cm, stopping the *Q*-function growth at the end of growth
SD	standard deviation
T	total height function in cm; *T(age) = Q(age) + E(age) + P(age) – S(age)*
T_{max}	modelled total adult height in cm, $T_{max}= E_{max}+ Q_{max} + P_{max} - S_{max}$
Tpubgain	$Tgain_{P5-100} = T_{max} - T(AgeP5)$
TageTonset	$T(AgeT_{END}) - T(AgeT_{ONSET})$

PERSONAL NOTES

This thesis is based on a PhD-research project carried out between 2013 and 2018. It started with a clinical interest in how children and adolescents grow. In particular, I was curious about generational growth patterns, if the correlations between children and parents in adult height could also be seen as similar growth patterns. This is sometimes noted clinically, when evaluating children of short stature or deviant growth, growing below their genetic potential. One or both parents may also have a history of being short as a child, however as adults often just slightly below average, not short statured from a medical/statistical perspective. In the beginning of my clinical carrier, my mentor Stefan Aronson first drew my attention to this phenomenon, surprisingly almost not studied scientifically. The pubertal growth spurt was another interesting topic, somewhat enigmatic when predicting further growth due to both the broad variation in time, and also due to variation in height gain during puberty. Previously, in my younger days I had started with two different research projects, without completing, I was now interested in a more long-term research commitment.

The research-project was initiated in 2012 when I contacted Professor Kerstin Albertsson-Wikland, with the knowledge of her as the principal investigator of the GrowUp 1974 Gothenburg study cohort. Meetings and discussions with Kerstin, Stefan, Aimon Niklasson, Dre Nierop and Lars Gelander followed 2012-2013, and in June 2013, I registered as a PhD-student. Already in 2012, I was introduced to what at that time was called “EQP”, a fascinating project under development, modeling human growth.

My PhD-studies have now come to an end. It has been very interesting to take part of the further development of the QEPS model, which has really evolved the previous few years. The broadening of the project with BMI (Lauren Lissner) also has been fruitful. My last year of the PhD-period has meant a lot of reading, really deepening my knowledge on human growth, sometimes quite far away on this broad topic. The last few months with a lot of writing have been hectic with very long days (and nights!) trying to complete, something most previous PhD-students have experienced. Still, I do not consider this the end of my research journey. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.

INTRODUCTION

Like most important aspects of human life, growth is the result of the combined impact of nature and nurture. The concept of growth outlined in this thesis relates mainly to height and changes in height and growth pattern over time in humans. Growth is the consequence of a dynamic process where molecular events in the cells, including cell growth, hypertrophy (increased size of cells), cell division and hyperplasia (increased numbers of cells), are translated into elongation of bones at the epiphyseal plate (growth plates), leading to increased stature in the human being. Broadly speaking, human growth can be divided into different stages known as growth periods: fetal, infancy, childhood and puberty. The fastest period of growth is before birth. After birth, the velocity of growth starts to decline gradually over time. Growth continues to be rapid during early infancy, reducing in velocity throughout infancy and childhood until the start of puberty. The pubertal growth spurt begins with an accelerating phase of growth and ends with a progressive slowing of height velocity that continues until adult height is attained (Figure I.1).

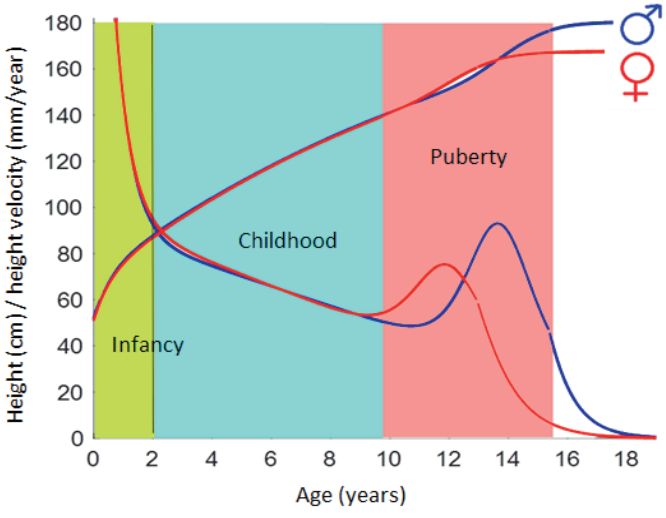


Figure I.1.Height and height velocity curves from birth to adult height. The shaded areas show the periods of infancy (green), childhood (light blue), and puberty (light red). The colours indicating mean ages for girls, in boys, puberty is about two years later.

All newborn babies have the genetic potential to grow, being born with a map for further growth influenced by hormones and environmental factors. The genetic map is the result of the combination of genes from both parents at conception. Many different genes are involved and, with the exception of

monozygotic twins, each individual has a unique mix of genes. The individual genetic map may resemble that of one parent (or grandparent) more than the other, depending on which genes are expressed. During fetal life, there is rapid cell division, resulting in growth; this is influenced mainly by the size of the mother, the size of the uterus, nutritional supply and other factors that affect the mother and foetus during pregnancy. Thus, various environmental factors have an impact on the size of the baby at birth. During infancy, childhood and puberty; hormones and external influences, including diseases, nutrition and psychosocial circumstances, cause variations in growth patterns. In the last decades, a role for epigenetics in explaining variations in human growth has also been recognised. Epigenetic markers, which may be inherited or result from the influence of hormones or other external factors, impact on the way cell proteins process different parts of the DNA. As such, they have the potential to alter the expression of genes in the body by affecting the way in which the genetic map is read.

Knowledge regarding human growth has evolved during the last two centuries, and has been of particular importance for those working in anthropology, paediatrics and public health. The study of human growth – also known as auxology (from Greek αὔξω, auxō, "grow"; and -λογία, -logia, science) – now involves contributions from a wide range of disciplines including anthropology, paediatrics, genetics, cell biology, physiology, endocrinology, neuroendocrinology, epidemiology, public health, nutrition, ergonomics, archaeology, history, economic history, economics, sociology, and psychology. This thesis contributes to the area by analysing growth patterns.

The concept *growth pattern* has no clear common definition. One definition could be the *repeated or regular way in which something happens* (I). Growth patterns, by this definition, refer to the sequential order in which height changes in growing individuals, a universal pattern of intrauterine, infancy, childhood and pubertal growth. In this case, tempo (time) and amplitude variations (i.e. height or weight) generate individual growth patterns. A pattern could also mean *a guide when something new is created* (II). If growth is connected with pattern in this context, the result resembles the first common pattern definition. These two definitions can be applied to individuals, where growth trajectory is synonymous to growth pattern. *Growth trajectory* means the path, the change in height (amplitude) over time

(tempo) from the new born to adult height. Another definition could be an arrangement of lines or shapes showing different visual appearances (III), like the distribution of a growth variable in a group. Growth patterns may also mean a reliable sample of observable growth characteristics (IV). The latter two definitions may be appropriate when defining and studying groups, sub-groups or populations, where all individual measures together shape the population pattern.

The framework and underling papers reported here detail the creation and testing of a new growth model, QEPS (Quadratic–Exponential–Puberty–Stop). The QEPS model can both create individual growth curves from measures of height and separate growth into different functions, allowing for comparisons of growth patterns between individuals and groups. The methodological paper describing the QEPS model is added as supplemental information at the end of this thesis (1). QEPS allows detailed description and exploration of the pubertal growth spurt (Paper I/*QEPS-puberty study*) and the relationship between body mass index (BMI) in childhood and further growth (Paper II/ *QEPS-BMI study*). The thesis also deals with secular changes; exploring changes in adult height and height attained during infancy, childhood and puberty across the last four decades in the Nordic countries, and across seven decades for adult heights in Sweden. (Paper III/ *Nordic height study*). The last paper is based on detailed analyses of changes in growth patterns in Sweden over a 16-year period (Paper IV/ *Growth pattern study*). A general view of the regulation of human growth, explained in more detail in the following sub-chapters is presented in Figure I.2.

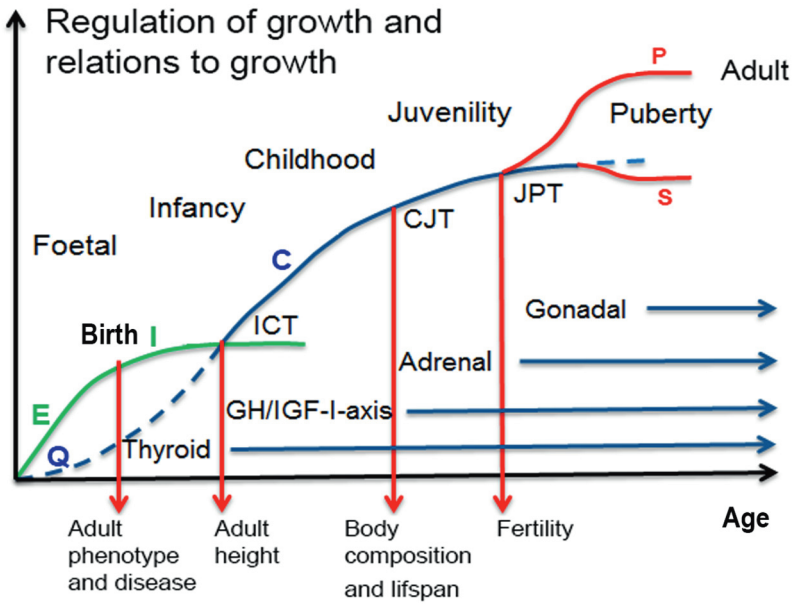


Figure I.2. Generalized view of human growth. Human growth can be mathematically divided into separate phases: *Foetal/Infancy, Childhood, Juvenility & Puberty*, during which growth is differently regulated by hormones. Transition between each of these growth phases is associated with increased cellular plasticity and the activation of the hormone axis that regulates growth during the phase to come. Environmental factors such as nutrition, disease and social status are known to have a major epigenetic impact on the regulation of growth during periods of transition. 1. A mathematical growth model can capture the different components of growth, and be used for testing hypotheses of regulation. Two models, *ICP* and *QEPS*, can describe growth from foetus to man. 1.The foetus/infancy growth phase, can mathematically be divided into (*Q)uadratic & (E)xponential* functions of the QEPS model, both of which start during early foetal life, or Infancy in the ICP model. Size at birth and infancy growth determines the long-term metabolic, cardiovascular, cognitive functions and mortality; 2. The *ICT* i.e *Infancy/Childhood Transition* from the nutrition-dependent foetal/infancy into the GH/IGF-I axis dependent childhood will determine adult height; each month of ICT-delay leads to a loss of 0.5 cm in adult height. 3. The childhood growth phase is GH dose-dependent; the GH-dependent C- or Q-function growth represents the net result of the individual balance between GH secretion and GH responsiveness; 4/5:The *Childhood/Juvenility/Puberty (C/J/P) transition* from the GH-dependent childhood period to the GH/sex-steroid-hormone-dependent *Pubertal growth phase* with a specific P-function growth, begins with the *Childhood /Juvenility transition* which is accompanied by the onset of the adrenal steroid hormones which determine body composition and longevity. This is followed by the *Juvenility/Puberty transition* and the onset of the gonadal steroid hormones that induce pubertal development, determine fertility and mature cognition and in high levels will close the epiphyses which ends growth in height.
With courtesy from Professor Kerstin Albertsson-Wikland.

1.1 WHY IS HUMAN GROWTH OF INTEREST?

A general interest

Many people are interested in questions concerning human growth; parents, in particular, are often curious and sometimes worried about the growth of their children. Growth is something all humans experience. Being tall or short, thin or fat, entering puberty early or late, are often essential parts of an individual's identity. Questions of stature have influenced the human language, and concepts of height, have meanings beyond their original distinction in various different languages. Philosophical and scientific thoughts on human growth have probably been part of humanity for many thousands of years, and there are documented discussions and theories of growth in humans from the civilizations of ancient Greece, Rome, China and India (2, 3).

Detection of diseases or psychosocial problems

From a medical and public health perspective, growth in childhood is used as a measure of integrated health; deviations in growth from a predicted trajectory often signal disease and/or psychosocial problems (4, 5). The current medical paradigm of monitoring growth (both height and weight), is based on the premise that; (I) it allows early detection of poor growth and identification of causal factors, and (II), that children found to be growing normally are likely to be in generally good health. The belief that taller children are healthier than shorter children has been debated for centuries (3). As long ago as the 1770s, Duke Carl Eugen of Württemberg recognised that increases in height over time, height velocity, would reflect individual health status better than the actual height attained (3) .

Growth in individual children has been monitored to detect diseases and signs of a sub-optimal environment since the late 19th century (for details see chapter 1.9). In more recent times, the World health organization (WHO) has prioritised regular growth monitoring for children all over the world and has emphasized; "children's right to achieve their full genetic growth potential" (6). At various points in history, and still today, poverty and poor sanitation put populations at increased risk of under nutrition and infectious diseases,

which are both major causes of impaired growth (7, 8). Growth failure in a child can be a sign of feeding problems, psychosocial problems, and numerous chronic diseases such as asthma, cystic fibrosis, kidney-failure, and heart disease, as well as endocrinological disturbances, rheumatic diseases and gastro-intestinal disorders (8-20). Short stature and a slower than expected height velocity, may also be signs of musculo-skeletal disorders and conditions as Turner syndrome and Silver–Russell syndrome (21-24).

In the 1960s, James Mourilyan (Jim) Tanner formulated the fundamental questions that are still essential today in the assessment of individual growth (25). Is the child of appropriate size for his/her actual age? Is the height velocity appropriate? A third question applies where there has been some kind of intervention: have the actions taken to optimize the child's health given rise to appropriate growth? More details concerning growth monitoring are presented in chapter 1.9.

The fact that the growth of a child is not just a measure of present and past conditions, but may also be important for future health, has been recognized during the last decades. Childhood obesity, in particular, is a major health concern, seen nowadays as an epidemic. Obesity in childhood is associated with a high risk of continued obesity in adulthood and an increased risk of cardiovascular disease, type 2 diabetes, psychiatric/mood disorders and musculoskeletal problems (26-28). The Norwegian general practitioner Anders Forsdahl noted in the early 1970s (publications in Norwegian language) that an elevated risk of cardiovascular disease was associated with poor living conditions during infancy and childhood (29, 30). Later, the "Barker hypothesis" presented in 1986 showed that suboptimal growth in utero and during infancy (mainly being born small/with low birth weight) can have adverse health effects later in life; suboptimal growth was associated with increased risk of hypertension, stroke, coronary heart disease and type 2 diabetes (31-33). Inappropriate weight gain with following low height gain (failure to thrive, FTT) will have great importance as discussed in chapter 1.7. Thus, monitoring growth may also allow intervention in infancy/early childhood to optimize health in a life-course perspective.

Today, numerous published studies have shown that adult height is related to morbidity and mortality in later life. In general, risk of cardiovascular disease and overall mortality are associated with short stature (34-37), and risk of

cancer is related to tall stature (35, 37-41). Suicide risk (both attempted and completed) is increased in men with impaired linear growth in fetal life and short adult stature (42-44). The timing of puberty and amount of growth during puberty are also associated with future health and disease. Many studies have shown adverse outcomes associated with early puberty in females, with increased risks of obesity, type 2 diabetes, cardiovascular disease, and breast and gynecological cancers (45-48). In males, early puberty is also associated with adult obesity, cardiovascular disease, bipolar disorder and depression (46, 49). In contrast, a late onset of puberty is related to increased risk of osteoporosis in both sexes, cervical cancer in women and psychiatric problems (anxiety, bipolar disorder and depression) in men (46, 50).

Psychological, sociological and economical aspects

Heightism – prejudice or discrimination based on height, has been recognized as a potential problem. The concept of heightism was created 40 years ago, but the phenomenon has probably been prevalent for much of human history. Like other prejudices, it can be conscious and openly expressed or subconscious (51). Studies have shown that tall men are more likely to be married and have more children than shorter men (52, 53). Inverse relationships have been found for women born before 1965 (fewer marriages in tall compared with short women), with no clear association regarding marriage and height in women born after 1965 (54). Other studies have also shown that very tall women, in particular, but also very tall men are less likely to be married (55-57). In both sexes, tall stature is associated with having attained a higher level of education (58-60). Several reports note that taller people have higher incomes than shorter people; however, findings may be confounded by other factors such as education and social background. Nevertheless, studies have shown that significant correlations with height remain after adjustment for confounders (37, 58, 61, 62).

When studying height in childhood and psychosocial outcomes, measures of quality of life and self-confidence are divergent. Children first become aware of their relative stature from around 7–9 years of age (earlier in girls than boys) (63). In general, population-based studies do not find significant associations between height and measures of friendship, self-esteem or reputation with peers; whereas clinical studies often find correlations between short stature and low self-esteem/psychosocial problems (64-70).

At the population level

All individuals in a defined area at a certain time constitute the population. The height of a population can be followed over time to analyse differences between countries. Generally, tall stature is associated with sufficient nutrition, good living conditions, good economic development and few diseases during childhood (4, 7, 71). The mean height of a population can broadly be related to socio-economic conditions (71). Besides correlation between average height and growth domestic product (GDP) per capita, there is also evidence that socio-economic equality is important for attained adult height (72, 73).

A different view - advantages of a shorter and smaller body size

In both scientific circles and life in general, the axiom for centuries has been that being tall is beneficial. However, there are many advantages to being short and having a small body size. From a global perspective, there are ecological benefits in terms of utilisation of food and water resources, resulting in less environmental impact, including lower greenhouse gas emissions, in a world of shorter, smaller people as opposed to taller, larger people (74, 75).It has also been hypothesised that, as populations move closer to reaching maximum genetic height potential, there is a parallel increase in the risk of developing chronic diseases (76). This is borne out by data described above showing that the risk of malignant diseases is increased in those with tall compared with short adult stature. Being short as an adult may also be associated with a lower risk of malignancies relative to taller peers, and there is also evidence that being short during childhood is associated with a lower risk of malignant melanoma in adult life (77). The association between short stature and cardiovascular disease may be linked to socio-economic differences; after adjustment for socio-economic factors, the impact of short stature disappears or is diminished (42). When studying centenarians (individuals of above 100 years of age) on Okinawa, an island outside the Japanese mainland they were in general short or very short, demonstrating the potential advantages of being short for increased longevity (75, 78). Short stature is correlated with increased relative strength, greater endurance and faster reaction times, and is beneficial in some sports and professions (79).

1.2 GROWTH DURING FETAL LIFE, INFANCY & CHILDHOOD

Growth in utero

The fastest period of growth is before birth. Intrauterine growth is rapid, especially during the second trimester of pregnancy (weeks 13–28) when longitudinal growth rate is extremely fast; length increases from 2.5 cm at the beginning of the second trimester to 35 cm at the end (80). The genetic component of growth at this time is weak compared to other growth periods; the correlation between length at birth and parental height ranges from 0.15 to 0.33 (81-83). From studies of pregnancies following egg donation and surrogate motherhood, is it known that birth size correlates more closely with the stature of the surrogate mother than the genetic mother/egg donor (84). The regulation of foetal growth remains enigmatic (Figure I.3).

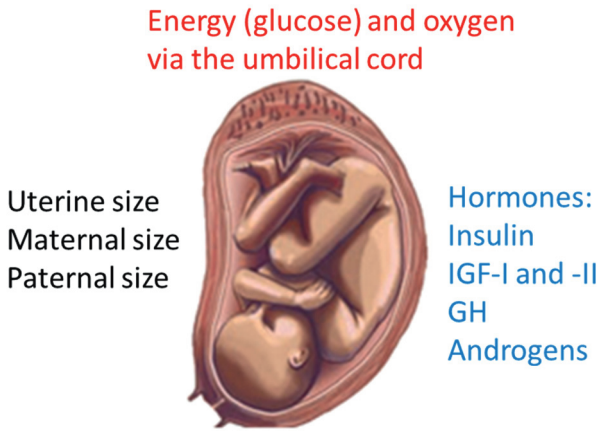


Figure I.3. Foetus in utero with different factors affecting intra-uterine growth (both weight and length).

No key circulating hormone has been identified. Length at birth in infants who lack thyroid hormone (thyroxine) does not differ substantially from other newborns, likely due to the effects of maternal thyroid hormones passing through the placenta. Infants with growth hormone (GH) deficiency are on average 1–2 cm (2–4%) shorter at birth than unaffected infants (85-87). Whether this slightly reduced birth length is secondary to the lack of

metabolic effects of GH via insulin-like growth factors (IGFs), or to the lack of a direct effect of GH on cartilage, is unclear (for the actions of GH see subchapter *Childhood growth period*). Maternal size (especially uterine size), paternal size, nutritional support and oxygen level, together with IGF-I and -II, are believed to be important for fetal growth (80, 88, 89). Boys are generally heavier and 0.5–1.5 cm longer than girls at birth (90-93). This difference is thought to be due to higher intrauterine levels of androgens (90, 91).

Many conditions can affect intrauterine growth; diseases of the mother, maternal diabetes, and lifestyle factors such as smoking, with nutrition and placental blood flow as common denominators. Maternal diabetes (higher levels of blood glucose/more energy) leads to enhanced growth, whereas the other circumstances mentioned are linked to decreased growth (88). Despite this, there is evidence that intrauterine influences do not have a major impact on adult height, as both children exposed to intrauterine starvation in Leningrad and during the Dutch Famine of world war II (WWII), attained normal adult height, independently of when in gestation the famine occurred (94, 95). In babies born extremely preterm (less than 28 weeks GA), nearly all children were close to normal height when they started school, and parental height was the factor explaining most of the variation in height at 7 years of age (96). Even in children born before 26 weeks of gestation was the height at 10 years of age just 0.3 standard deviation scores (SDS), approximately 2 cm, below expected height based on the height of the parents (97).

Infancy growth period

Infancy is generally used to describe the first 1–2 years of life. The first year of life can be seen as an extension of the intrauterine growth period; growth continues to be rapid, although growth rate is gradually declining over time. Length increases on average by 24–28 cm during the first year of life, with babies growing from 46–54 cm at birth to 70–82 cm at 1 year of age (92, 93). The increase during the second year of life is a little less than half of the amount attained during the first year. The sex difference observed at birth remains stable; boys continue to be about 1 cm longer than girls during infancy. Growth during infancy is mainly dependent on nutrition, thus

feeding problems or diseases leading to insufficient nutrition can be devastating, and may have lifelong consequences including stunted height (see *Infancy* in chapter 1.7). Stunted growth is defined as short stature, with height below –2 SDS relative to the height reference that shows the expected height in a healthy population of the same age (see chapter 1.8 Figure I.24 and growth references). Hormonally, growth during infancy is regulated by thyroxine and the IGFs. Infants with hypothyroidism (lack of thyroxine) develop pronounced growth failure (18). During the infancy growth period, an adaptation to genetic height potential is often seen; infants with tall parents typically grow more than average, with the reverse pattern being seen in infants with short parents (98).

The transition from infancy to childhood (infancy–childhood transition, ICT) is an important window, both for growth during childhood and for later development (99). ICT is a concept that comes from the infancy–childhood–puberty (ICP) growth model (see chapter 1.8 for more details). The timing of ICT is of importance for adult height; a later transition relative to peers is associated with shorter adult height (100). As a consequence stature at 2 years of life is predictive for future gain in height and the adult height that is attained (82, 101). At 2 years of age, the correlation between current height and adult height is 0.8; an increase of about 0.5 since the correlation with length at birth. Similarly, height at 2 years of age correlates well with parental height (r^2 = 0.7–0.8) (82, 83, 101).

Childhood growth period

Childhood growth generally includes the period from 1–2 years of life until the start of the pubertal growth spurt in adolescence. Height velocity usually declines slowly or remains stable throughout childhood. As the childhood growth period lasts for a long time (range, 7–12 years), growth during childhood is important for adult height. A general summary of patterns of linear growth, alongside the important factors for growth during infancy, childhood and puberty, can be found in Figure I.2.Nutrition and psychosocial factors remain important for the regulation of growth during childhood, although they are not as crucial as they were in infancy and hormones becomes more important. Cortisol from the adrenal gland and thyroxine act as permissive hormones and are necessary for normal growth and

development; they have both a direct action on growth via the growth plate of the long bones, and an indirect action via regulation of the GH–IGF-I axis (102-105). The GH–IGF-I axis plays an important role in childhood growth.

GH has a dual effect, by both acting on growth plate receptors and enhancing the levels of IGF-I at the growth plate. GH and IGF-I stimulate linear growth at the growth plate (Figure I.4). The growth plate is a thin layer of cartilage, found in most bones. At the growth plate, chondrocytes proliferate, undergo hypertrophy and generate new cartilage, which is in turn, remodeled into bone tissue (106, 107). The result is that new bone is created progressively at the growth plate, causing bones to grow longer (108).

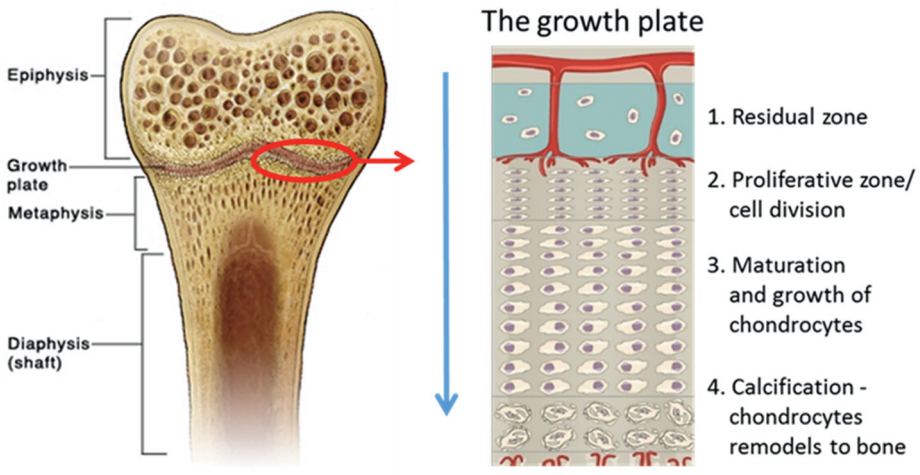


Figure I.4. Long bones and growth plates. A typical long bone (femur) is shown on the left with the different parts of the bone labelled. To the right is a detailed view of the growth plate showing the three histologically and functionally distinct zones; the resting/reserve, proliferative and hypertrophic zones. The chondrocyte matures from top to bottom with resulting calcified matrix (solid bone).

GH is secreted from the anterior pituitary under the regulation of the hypothalamus; GH secretion is stimulated by the pulsatile release of GH-releasing hormone (GHRH) and inhibited by the constant secretion of somatostatin (109). GH is secreted in a pulsatile pattern, with peaks – high levels of GH in the blood stream – every third hour that occur in synchrony with GHRH peaks, with troughs – low or undetectable levels of GH in the blood in between (Figure I.5) (109, 110). During childhood and puberty, the amplitude of GH peaks, and thus the GH secretion rate is higher than at other times during the growth period, and peaks have higher amplitudes during the

night than the day. GH secretion rates correlate with height in children, although height being the net result of the balance between GH secretion and GH responsiveness. (111-113). There is a negative feedback loop by which high levels of IGF-I reduce GH secretion. GH secretion is stimulated by short-time stress, hypoglycemia and amino acids as arginine (109, 114). The secretion of GH is reduced by high levels of insulin, glucose and fatty acids (115).

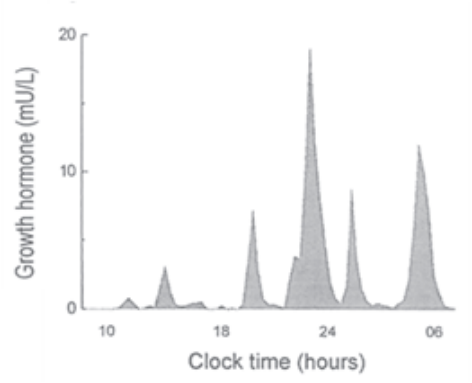


Figure I.5. Example of 24-hour growth hormone (GH) profile of a child with short stature. Continues blood withdrawal system gave integrated 20 min samples for GH-analyses. The pulsatile pattern of GH secretion with peaks of higher amplitude during night than day, and with low/undetectable levels in-between.

A consequence of the way in which GH is regulated is that short-term fasting promotes GH secretion, whereas long-term periods of insufficient nutrition and/or psychosocial stress, reduce GH secretion (116). Psychosocial deprivation thus may mimic GH deficiency, with reversible GH insufficiency, normalising after the child is separated from the adverse environment (117). Glucocorticoids (anti-inflammatory agents), often used in acute and chronic inflammatory diseases such as asthma, rheumatism and Crohn's disease, slow down linear growth via direct actions on the growth plate (118, 119). It cannot be over emphasized, that the effect of a hormone not only depends on what can be measured relatively easily, i.e. hormone levels, but also the sensitivity of the tissue, where different expression of receptors (both amounts and function of receptors) in the target tissue is important. Regarding GH, the GH-receptors ability to act from its binding to GH is defined as sensitivity, while the ability to determine the entire signaling toward a certain effect is defined as responsiveness (112).

With respect to growth, childhood is the period generally characterised by slowly declining height velocity. Somewhat puzzling, some children have a period of accelerated growth during mid- or late-childhood; where this occurs, it is known as the "mid-childhood spurt" (120). Late childhood

(around 6–9 years in girls and 7–11 years in boys) is sometimes called juvenility, particularly in psychological research and in evolutionary theories of human growth (see chapter 1.4). The juvenility period or the mid-childhood spurt has not been recognised as a separate growth-function in neither the ICP model nor the QEPS model. The mid-childhood spurt may coincide with the secretion of androgen, androstenedione and dihydroepiandrosterone (121). In fact, signs of the actions of androgen, such as oily skin, adult-type sweating, body odor and sparse pubic hair, are seen in some children during these years (clinically called premature adrenarche/pubarche) (121, 122).

Growth patterns – short term: catch-up growth

Catch-up growth is a physiological phase of temporarily increased growth velocity, after a period of declining growth (Figure I.6). Andrea Prader and Jim Tanner, who showed that children with many different conditions affecting linear growth, experienced increased growth during recovery/ treatment introduced the concept of catch-up growth (18, 123).

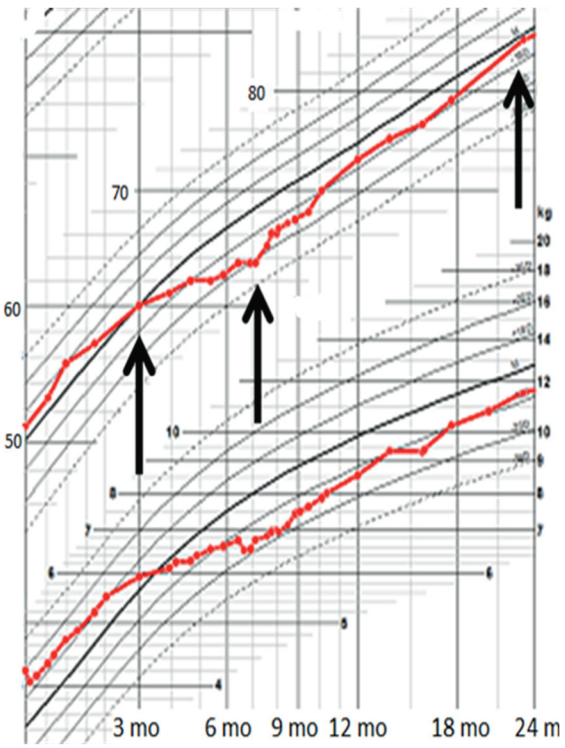


Figure I.6. Growth curves of a girl showing catch up growth. Red lines show length/height in cm (top) and weight in kg (bottom) of a girl from birth to 2 years of age. These are plotted on a Swedish growth charts with mean, ± 1-3SDSs (standard deviation scores). Height/weight (cm/kg) on y-axis, age on x-axis. The height of the infant remained in line with the mean height expected based on age until 3 month of age (first black arrow) thereafter the growth rate arrested. At 7 month of age, the infant was diagnosed with acquired hypothyreosis, at a length of –2.1 SDS (second black arrow) and treatment with thyroxine was started. At 23 months of age, the child had experienced catch up growth; height was now –0.1 SDS (third black arrow). Growth curve from the Department of Pediatrics, Kungsbacka, Halland Hospital, Sweden.

Catch-up growth is defined as an increase in growth that takes a child in whom growth is impaired back to the original growth track i.e. the SDS position on the growth chart that their height velocity was following (see chapter 1.8). The term can also be used for children whose growth returns naturally to the expected course or whose growth is improved by treatment with GH (124). Children born small for gestational age (SGA) may also be said to show catch-up growth, when growth moves to their genetic potential; actually, 90% of infants born SGA experience a postnatal catch-up (125). Catch-up growth has been seen during infancy and childhood for premature and extremely premature babies (96, 97).

At a community level, catch-up growth was noted during childhood and adolescence in school girls in Oslo following the progressive decline in height during WW II by the former prime minister of Norway/WHO Director general, Gro Harlem Brundtland. She found that, there was normalisation (catch up) of mean height in schoolgirls, with height during childhood and adolescence returning to pre-war levels, without affecting adult height (126).

Growth patterns – ultra short term: Mini growth spurts

The general assumption that longitudinal growth is continuous in *healthy* infants and children is not true based on detailed analyses of short-term growth. From studies with knemometers (measuring lower leg length) in particular (Figure I.7), there is evidence that growth occurs in periods, with mini growth spurts lasting days or weeks, followed by periods of nearly no growth (127-131).

Figure I.7. Picture of a child in the sitting knemometer. Photo curtesy of PhD Samuel Urlacher.

This pattern of discontinuous growth may be related to variations in the GH action, either in the secretion of GH or GH responsiveness (111, 132, 133). The nature of short-term growth can also be studied using radiolucent implants in long bones (see chapter 1.8) (134, 135). The precise distributions of mini growth spurts and resting periods are still largely unknown; however, it has been shown that mini growth spurts exists in both infancy and childhood (127, 128, 136).

Growth patterns – Seasonal variation in growth

The fact that variations in height velocity may be related to the season of the year was first reported by Buffon in 1799 (137). Almost 100 years later, the Danish priest Malling-Hansen was engaged, besides inventing the first typewriter, in extensive studies of daily height and weight measurements of children at the Royal Deaf and Dumb Institute in Copenhagen. He found that there were three periods of height gain during the year; a minimum period, from mid-August until the end of November; an interim period, from the end of November to the end of March; and a maximum period, from the end of March to mid-August (138).

There were also three periods of weight gain during the year, which were inverse in pattern to the periods of height gain. Malling-Hansen searched for causes; comparing air humidity, the phases of the moon and variations in air

pressure. The research topic was of interest to many auxologists in the US and Europe during the following decades, and although some studies showed only minor seasonal variations in height gain, most studies reported similar patterns to those observed by Malling-Hansen, but with wide intra-individual variation. In a Swedish thesis from 1929, it was reported that boys exposed to sunlamps during the winter gained 15 mm more height than unexposed controls (139). In the 20th century, it was recognised that there was a relationship between height gain and sunlight, with the most pronounced seasonal differences in growth being observed close to the polar zones where the variations in day light are considerable (136, 139-141). Furthermore, it was noted that there was no seasonal variation in growth in blind children, questioning whether it is sun-exposed skin or the influence of light on the central nervous system (CNS)/pituitary that is of importance (141).

In the *one year growth study* from Gothenburg (Gelander et al.), it was shown that seasonal growth variations correlated with levels of IGF-I and GH-binding protein, but not urinary GH excretion (133, 142-144). Examples of lower leg length curves are seen in Figure I.8. A more recent study found seasonal variations in vitamin D levels, suggesting another link between light and height gain; vitamin D, essential for normal bone growth, is mainly synthesized in the skin following exposure to sunlight (145). In tropical and sub-tropical regions, different seasonal patterns in growth have been observed, possibly secondary to shortage of food after periods of drought or related to differences in sunlight between dry and rainy seasons (146).

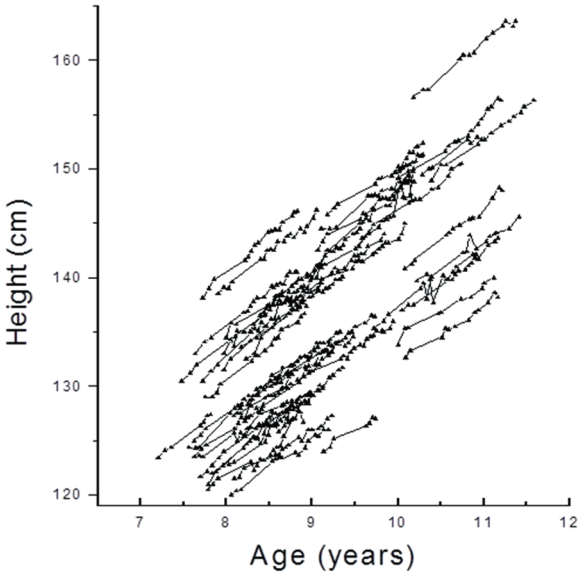
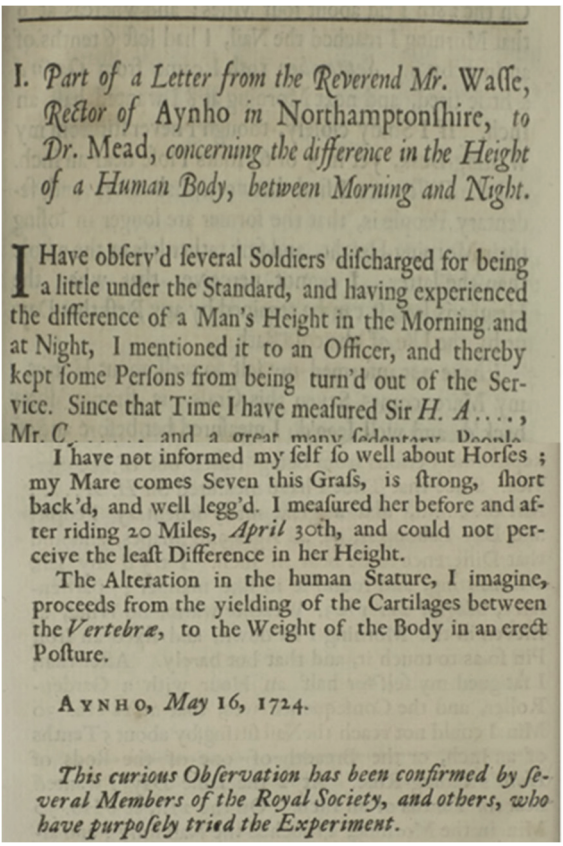


Figure I.8. Lower leg length curves. The figure shows non-linear growth in the 7-12 years old heathy boys participating in the "One year growth study" measured monthly using a knemometer. Gelander, L (133).

Diurnal variation in height

Standing height decreases over the course of the day. In the 16th century, French folklore said that growth occurred at night and that children were taller in the morning than in the evening (3). In UK, the priest Joseph Wasse observed height loss throughout the day, and noted that the loss in height was greater in individuals doing heavy work, and absent in his horse (Figure I.9). He interpreted that the loss in height was related to the back, not the legs (147). Malling-Hansen was the first who systematically studied diurnal postural variation in children; he found that body height decreased by about 10 mm over the day (138). In the 20th century, diurnal variation in height has been quantified as being between 6 and 12 mm in different studies (148, 149). Variation may be reduced by use of the stretch technique (see chapter 1.8), where the mean difference between 09:30 and 14:00 h was 2 mm, increasing to 5 mm between 10.00 and 17.00 h (150). However, the clinical usefulness of this method has been questioned (151). Today, postural changes in height through the day are largely thought to be due to spinal disc compression.



I. *Part of a Letter from the Reverend Mr.* Waſſe, *Rector of* Aynho *in* Northamptonſhire, *to Dr.* Mead, *concerning the difference in the Height of a Human Body, between Morning and Night.*

I Have obſerv'd ſeveral Soldiers diſcharged for being a little under the Standard, and having experienced the difference of a Man's Height in the Morning and at Night, I mentioned it to an Officer, and thereby kept ſome Perſons from being turn'd out of the Service. Since that Time I have meaſured Sir *H. A*...., Mr. *C*..... and a great many ſedentary People

I have not informed my ſelf ſo well about Horſes; my Mare comes Seven this Graſs, is ſtrong, ſhort back'd, and well legg'd. I meaſured her before and after riding 20 Miles, *April* 30th, and could not perceive the leaſt Difference in her Height.

The Alteration in the human Stature, I imagine, proceeds from the yielding of the Cartilages between the *Vertebræ*, to the Weight of the Body in an erect Poſture.

AYNHO, *May* 16, 1724.

This curious Obſervation has been confirmed by ſeveral Members of the Royal Society, and others, who have purpoſely tried the Experiment.

Figure I.9. Description of diurnal variation in height. The letter from Reverend Wasse (147).

1.3 THE UNIQUE NATURE OF HUMAN PUBERTY

The pubertal transition

Puberty is a necessary step for human reproduction. Biologically, puberty is characterised by the transition from an immature child to a reproductively competent mature adult individual. The transformation is a complex process, caused by an interplay of hormones, mainly sex steroids from ovaries in girls and testes in boys. During puberty, secondary sexual characteristics develop; in girls, this involves the maturation of internal sex organs (ovaries and uterus), genitalia and breasts; in boys, this involves the maturation of genitalia (testes and penis). For both sexes, this results in the capability to mate and reproduce. During the pubertal transformation, there are typical changes in body composition, with increased fat mass and altered fat distribution in females (hips and breasts), and increased muscle mass in males. Other changes affect the skin, body hair, voice and brain structure. Pubertal development also includes an increase in height velocity, known as the pubertal growth spurt; during this period, the slowly declining height velocity of childhood is replaced by acceleration in height velocity. The increased growth occurs first in the peripheral bones, affecting the feet and hands. Later more rapid growth is seen in the long bones, ending with increased growth in the back, until the growth plates in all bones are closed and adult height is reached. All the changes associated with puberty take place during 4–6 years and have the consequence that girls and boys take on the typical appearances of mature females and males (152, 153).

The first clear sign of puberty in girls is normally breast-budding (thelarche). In clinical and scientific terms, the pubertal stages defined in the 1960s by Tanner are the gold standard for classification of pubertal development in girls. Breast stage 1 corresponds to prepuberty and stages 4–5 to full female maturation (entitled B1-B5) (152). During puberty, the ovaries develop, the uterus grows and external genitalia develop to mature appearance and function (154). The female milestone of puberty, the first menstrual bleeding (menarche) takes places in mid-puberty, typically 2–2.5 years after thelarche. The development of pubic and axillary hair typically runs in parallel with the pubertal development, although it is partly independent of gonadal activity,

being dependent on adrenal hormones (155). Pubertal stage 1 denotes no pubic hair and stages 4–5 full adult pubic hair (entitled PH1-PH5). Axillary hair is typically a later manifestation of puberty than pubic hair (152, 153). An overview of the pubertal maturation in females and males is shown in Figure I.10.

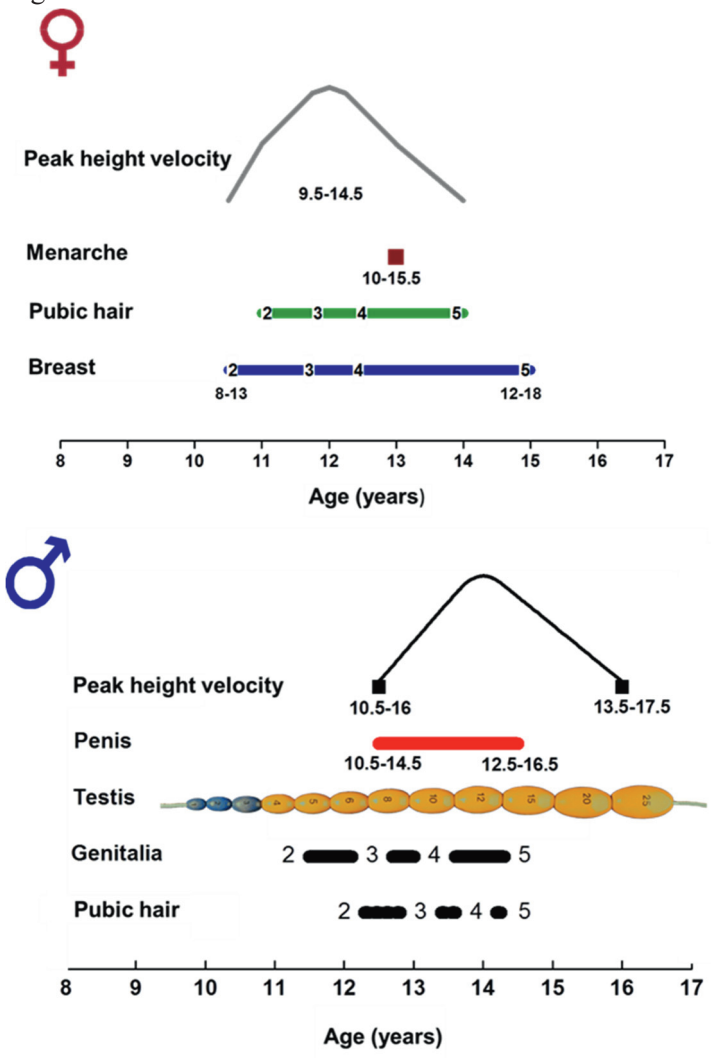


Figure I.10. Overview of pubertal maturation in females (top) and males (bottom). The figure shows the typical sequence followed by females and males during the pubertal transition. The numbers shown represent age range in years for the different stages/events (approximately ± 2 SDS). For boys, the volume of the testes is illustrated using a Prader orchidometer (blue/yellow) (156). Modified from an original presentation by Tanner, J, in "Growth at adolescence", Oxford, Blackwell Scientific Publications; 2.ed; 1962

In boys, the first sign of puberty is the growth of testicles, which increase from a prepubertal volume of 2–3 ml to 4 ml. This change is a less obvious than thelarche, and often progresses unnoticed. An early sign is also genital development, which develops from stage 1 in prepuberty to stage 5 at complete male maturation (entitled G1-G5) (153). Testicular volume is estimated using the orchidometer, which was first introduced by Prader in 1966; volume increases from the neonatal volume of 1 ml to 18–25 ml at complete masculinisation (156-158).

Hormonal changes in puberty –the onset

Late-infancy and childhood is characterised hormonally by silent gonadotropin-releasing hormone (GnRH) secretion, with low luteinising hormone (LH)/ follicle stimulating hormone (FSH) (gonadotropins) levels.

This pattern appears to be in common with apes, but different from most other mammals, which have only a short juvenility period before sexual maturation (159). The GnRH neurons extend from the hypothalamus to the pituitary. *Not going into puberty* is dependent on active inhibition achieved by CNS suppression of the hypothalamic–pituitary axis. The GnRH silence appears to be due to inhibitory CNS neurotransmitters, particularly GABA. Different G-protein-coupled receptors also appear to modulate the GnRH pulsatility (160). Abnormal embryonic migration of GnRH may lead to disturbed GnRH release/pulsatility. Genes associated with insufficient GnRH release have been shown to be involved in the migration of GnRH neurons. The *kisspeptin/GPR54* complex is one among many other genes/proteins working at the hypothalamic level as a pubertal regulator. Mutations/ variations in *kisspeptin* and *GPR54* (the receptor for kisspeptin) can result in both hypogonadism/late puberty and early puberty (161). The hypothalamic protein MKRN3 is another inhibitor of pubertal onset, where mutations cause central precocious puberty in both sexes, and declining levels of the protein is seen during late childhood/puberty (162-164).

When inhibition of GnHR secretion ceases, the cascade of puberty is started. In early puberty, increased amplitude of pulsatile GnRH secretion is seen (initially during late night), leading to increased FSH and LH secretion from the gonadotropic cells of the anterior pituitary gland (161, 165) (Figure I.11).

Why puberty starts when it starts is still an enigma.

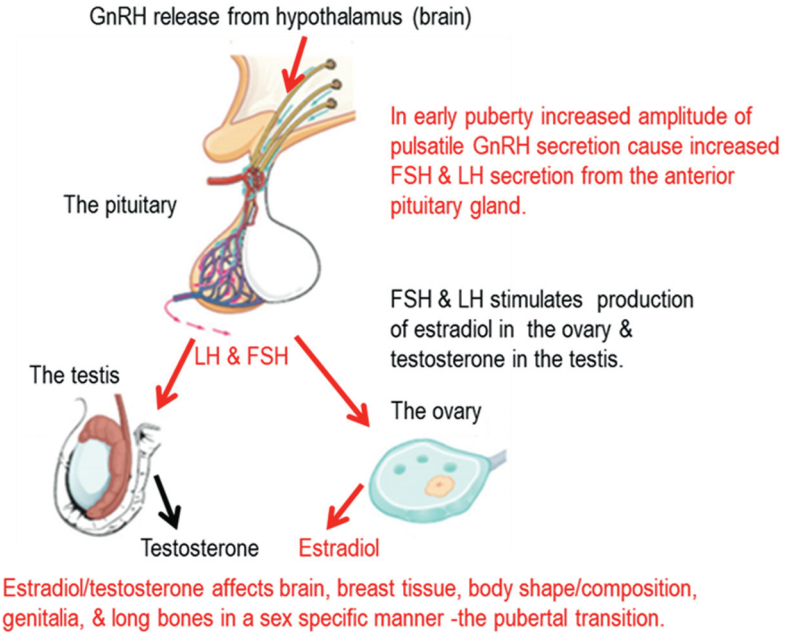


Figure I.11. Simplified overview of the endocrine regulation of puberty.

Hormonal changes during puberty –females

The endocrine starting point of puberty in girls is enhanced secretion of FSH during late night/early morning. FSH stimulates ovarian follicular development with estrogen production following. After the initial FSH rise, there is a progressive increase in frequency and amplitude of LH secretion. As puberty continues, sleep-related LH peaks last progressively longer and extend into the daytime. LH can increase 20–30 fold in amplitude, while FSH rises 3–4 fold (166). FSH induces activation of the enzyme aromatase in the ovaries; this enzyme aromatises the androgenic hormone androstenedione in the ovaries to estradiol. In the ovaries, FSH also induces production of progestin leading to development of follicles and upregulation of LH receptors. LH works together with FSH to stimulate estradiol production in the ovaries and, in late puberty, the monthly LH peak is essential for ovulation. The result of rising LH/FSH is an increase in serum estradiol levels with a peak midmorning, particularly in early puberty. As puberty progresses, the estradiol peak becomes both higher and broader (167). Levels of estradiol increase continuously during puberty, essential for both the

development of secondary sexual characteristics and the pubertal growth spurt. The secretion of estradiol stimulates estradiol receptors in the mammary glands, which results in an increase in stromal size (168, 169). Estradiol is also crucial for uterine development; estradiol stimulates growth of uterus by both hypertrophy and hyperplasia of uterine cells. The uterine endometrium continues to evolve owing to higher levels of estradiol (100–150 pmol/L) until the first bleeding, or menarche, occurs. Leptin, an adipocyte (fat cell) secreted hormone, important for energy balance, is present also in childhood, however important for pubertal development. Serum levels of leptin correlates with age, body fat, BMI and in females with pubertal maturation (170, 171).

During puberty, increased levels of estradiol lead to an approximate threefold rise in GH secretion (172). Estradiol acts both on hypothalamic–pituitary receptors to enhance the secretion of GH, and to decrease the inhibition from IGF-I on GH secretion (173). In addition, estradiol has direct effects on the growth plate via different estrogen receptors (174). Increased levels of estradiol in early/mid-puberty accompany accelerated growth, whereas high levels of estradiol in late puberty lead to maturation and fusion of the growth plate when all chondrocytes are remodeled into bone (175-177). Levels of estradiol throughout puberty in girls and boys are visualised in Figure I.12.

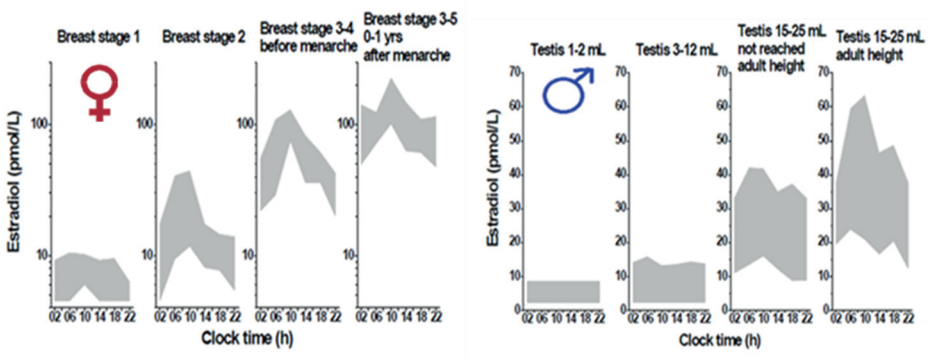


Figure I.12. Estradiol levels during puberty. 24-hour reference intervals for serum estradiol in girls (left) and boys (right) at different stages of pubertal development. Note the different scale on the y-axis for boys and girls. From Ankarberg-Lindgren, C, Norjavaara, E (167, 178).

Hormonal changes during puberty –males

For boys, the endocrine starting point of puberty is also enhanced secretion of LH and FSH during late night/early morning. LH stimulates the Leydig cells

in the testes to produce testosterone. FSH and intra-testicular testosterone stimulate the proliferation of seminiferous tubules and Sertoli cells starting spermatogenesis (161). Just like in girls, there is a gradual increase in frequency and amplitude of gonadotropin secretion during the progression of puberty (165). Levels of testosterone continue to rise in parallel with testicular development, following a diurnal rhythm, with the highest levels in the morning (179). Testosterone is the main functional hormone in male pubertal transformation, affecting the maturation of genitalia, increase in muscle mass and, together with adrenal androgens, the development of male body hair. In late puberty, boys have 15-times higher testosterone levels than girls (180). Testosterone is also partially converted into estradiol, initially without a diurnal pattern; high levels of estradiol during the morning hours are generally first seen during late puberty. During puberty GH secretion at least doubles due to the increased levels of estradiol (172). Estradiol exerts similar effects on the growth plate in males as in females, although levels of estradiol are much lower in boys than girls, and their source is different (181). In boys, the main source of estradiol is testosterone; 80% of estradiol is produced by peripheral conversion (aromatisation) of testosterone and androgen hormones. Testosterone can be converted to estradiol in adipocytes (fat cells). High levels of estradiol are seen at the end of puberty, closing the epiphyseal growth plates (178, 182). Individuals lacking functional estradiol receptors will continue to grow throughout adult life (183). High levels of estradiol also have a negative feedback on gonadotropin secretion (184). Levels of testosterone throughout puberty in girls and boys are visualised in Figure I.13.

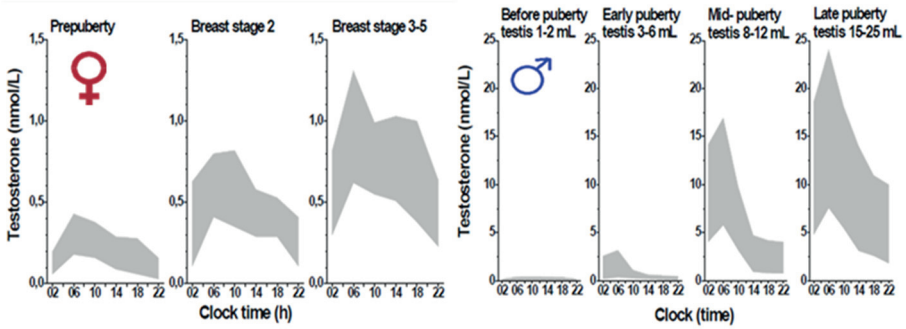


Figure I.13. Testosterone levels during puberty. 24-hour reference intervals for serum testosterone in girls (left) and boys (right) at different stages of pubertal development. Note the different scale on the y-axis for boys and girls. From Ankarberg-Lindgren, C, E. Norjavaara (180, 185).

The pubertal growth spurt

In puberty, the declining height velocity seen during childhood is replaced by an acceleration in height velocity signaling the pubertal growth spurt. Puberty is the period with the most rapid height velocity since infancy (152, 153). The pubertal growth spurt correlates with gonadal maturation, and is a consequence of the hormonal changes mentioned above. The growth spurt is, thus, an integrated part of the pubertal cascade of events. Height gain during puberty accounts for 20–35 cm in most healthy individuals, with boys in general having a greater gain than girls (186). Between 10 and 20% of the adult height attained is due to growth during the pubertal years (83). In individuals, growth during the pubertal years has an S-shaped pattern; subtle changes in the beginning, a mid-period of rapid growth with peak height velocity (PHV), followed by slowly declining growth until adult height is reached (Figure I.14).

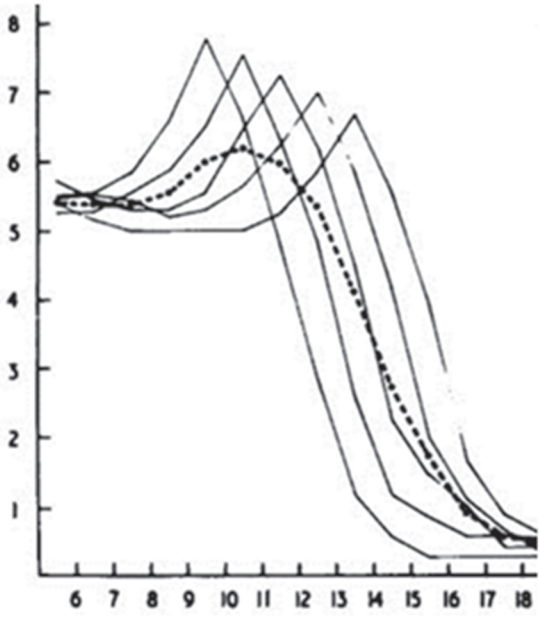


Figure I.14. Individual pubertal growth spurts. Height velocity in cm/year on the y-axis and age in years on the x-axis. Solid lines show height velocity during puberty for girls with different timing of pubertal growth. Peak height velocity (PHV) was typically more pronounced in girls who showed early compared to late pubertal growth. The dotted line represents mean PHV; mean values are always lower than observed in individual height velocity curves owing to variations in the timing of onset of puberty. From Shuttleworth, FK (187).

The growth spurt begins in girls around thelarche; girls may have increased height velocity some months before thelarche, or just after, when both breast budding and increased bone growth occur in response to increased levels of estradiol (152, 157, 175). PHV in girls is usually 8–10 cm/year and most often occurs at B2-B3 (152, 188, 189). Menarche is commonly seen about 1 year later than PHV at B3-B4 (152, 188, 189).

Boys generally have a steeper growth spurt than girls, with a higher PHV of about 9–12 cm/year; it occurs on average 2 years later than in girls (Figure I.1) (153, 188). Adult height is commonly attained approximately 2 years earlier in females compared to males. Thus, the resulting adult height difference between men and women (called sexual dimorphism of height) of 11–14 cm (72, 98, 101, 190), is the result of males being approximately 1 cm longer/taller from birth/infancy, experiencing a 2-year longer period of childhood growth, and gaining 2–3 cm more height during puberty than females. In boys, the pubertal growth spurt is noted first at testicular volumes of about 6 ml; a more discrete start than in girls (153, 188, 191). The breaking of the male voice is most commonly seen about the same age as PHV (188, 192).

Early or late puberty?

There is a wide variation between the sexes, between different populations and within a population in the timing of puberty. Aspects of pubertal timing are considered in relation to evolution, secular changes, genes/heredity and weight/BMI in other chapters.

Other mammals

Pubertal growth is unique to humans. Most animals (e.g. mice, rats and cattle), with the exception of humans and non-human primates, have a similar type of growth pattern; an S-shaped curve with only a single peak, that is, an initial acceleration followed by deceleration in growth rate (159). Humans differ from mammals like mice and cows in having the fastest growth rate in utero (other mammals grow fastest in infancy) and having a period of accelerated growth during puberty. In other mammals, sexual maturation occurs relatively soon after weaning. Other primates share with humans, a prolonged period of slowly declining growth, well before sexual maturation (juvenility). Some non-human primates also experience an adolescent growth spurt during which *weight* increases in one (in males: chimpanzees, *Pan troglodytes* and maybe orangutans, *Pongo*) or both sexes (in bonobos and gorillas, *Pan paniscus/Gorilla*) (159). No other primates have something that resembles the pubertal height gain seen in humans; this is probably due to lower sensitivity for estrogen in the growth plates, and possibly also due to hind leg length being shorter than made possible by bipedalism. Many mammals like mice, rats, cows and elephants continue to growth throughout life (the tallest elephants are 40–60 years old as seen in Figure I.15).

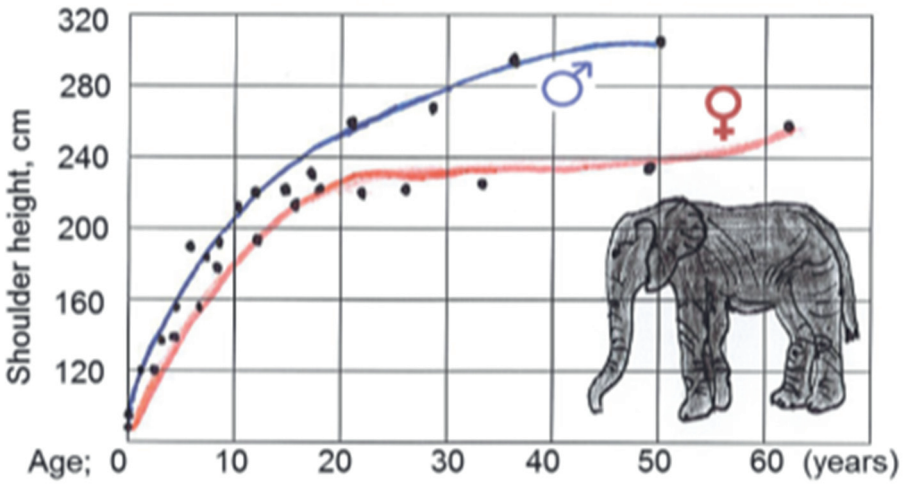


Figure I.15. Elephant growth chart. Shoulder height for male and female elephants according to age. Modified from Bogin, B (159).

1.4 EVOLUTIONARY ASPECTS OF HUMAN GROWTH

Life history approach

Evolutionary theories can be used to explore aspects of human growth. The way humans grow and evolve can be viewed in terms of trade-offs (compromises) between the evolutionary advantages and disadvantages of different traits (100, 193). Traits are shaped by natural selection to maximise reproductive fitness. Investing energy in one trait, for example, reproduction may generate many offspring but has disadvantages in terms of the quantity of energy allocated in raising those offspring. Compared to the offspring of other animals, humans are more immature as babies, and have a longer dependency on adults (even after weaning). Humans have a long period of post-natal growth, where the juvenility period is before sexual maturity, the juveniles in traditional (hunter-gather) societies are semi-independent of adults, followed by rapid growth during puberty and then some years later achieved reproductive capacity (159).

The transition between the four stages; infancy, childhood, juvenility and adolescence (puberty) can be seen as important stages for further growth, regulated by changes in endocrine activities (99). The transition periods can be modified in time (adaptation/plasticity) where the changed endocrine activities resulting in different patterns of growth are governed by epigenetic mechanisms. Delayed ICT (DICT) is seen as a way to survive in an energy restricted environment, resulting in lower energy demand with impaired growth and a shorter adult stature compared to earlier ICT (Figure I.2) (100).

The pubertal growth spurt in humans can be considered from an evolutionary perspective. During childhood and juvenility, growth is restricted as part of a trade-off to improve survival (less energy required). When the juvenile is more capable of obtaining food and contributing to the survival of the tribe, then the growth spurt can begin. For females, the pubertal transformation, and the pubertal growth spurt, were necessary in order for the female to attain a body size in which there is adequate space for the fetus to grow (193). For males, the pubertal transformation and growth spurt, resulted in a taller and more muscular appearance that was beneficial both in relation to external threats and fitness in competitions with other males to mate (99).

The sex difference in pubertal timing, with earlier and more obvious maturation in females, could be seen as females signalling reproductive capacity before they have actually achieved it. For males, the opposite picture is true; one theory is that this had the benefit of not being seen as a "threat" to older males in the tribe (193).

The trend for the onset of puberty to become earlier over time has also been analysed from an evolutionary perspective; again, the timing of puberty (the juvenility–adolescence transition) may be explained by a trade-off. Two fundamentally different theories have been proposed.

One, by Gluckman and Hanson, suggests that evolutionary strategies for greater reproductive fitness could account for the current early onset of puberty (194). For the last few generations it has been possible to give birth to, and raise more children than before; earlier puberty facilitates this development. The other, by Hochberg and Belsky, proposes that early puberty can be seen as an adaption to (negative) early life experiences during infancy and childhood. Unsecure rearing conditions may lead to a "*live fast, die young"* adaptation, where pubertal maturation is early to secure reproduction (195, 196). Both psychological and sociological studies, together with experiments in animals, present evidence in support of this theory (195, 197). These two partially opposing theories may both be true if timing of puberty is seen as an U-shaped pattern (stress on y- and age on x-axis), where sub-optimal conditions/environmental stress in utero, infancy and childhood lead to either very early or very late puberty, depending on *when* and *which* stressors are occurring.

Archeology, what can we learn from ancient bones?

During prehistoric and historic ages, osteological findings give evidence that human stature has changed; both periods with increasing and decreasing heights have been seen. When humans became farmers some 10,000–1,000 years ago, there was a general decline in stature compared to the previous 100,000 of years in hunter-gatherer societies (198). In Northern Europe, stature was then generally increasing slowly, and periods of climatic change may have contributed to both upward (milder climate) and downward trends (the "little Ice-Age", the cooling period in the 6th and 7th century AD) (199). Cultural changes probably also resulted in upward and downward changes in stature during pre-historic times. In Scandinavia, mean adult height in the first decades AD was 167 cm for females and 176 cm for males (200). From the end of the medieval time until the beginning of the 19th century, there was a decline in height in Europe. In Japan increased height from about 159 cm in 100 B.C. to a mean of 164 cm (800-1200 AD), followed by a decrease to 156 cm between 1600-1870 (201). In South America, the colonisation by Europeans was associated with a significant decrease in the stature of the native populations over several decades; height only began to increase at the beginning of the 20th century (202). Osteological findings give less evidence of changes in pubertal timing compared to secular changes in height; however measurements of long bones and pelvis can give some indications of when puberty occurred in pre-historic and historic times (203).

1.5 SECULAR CHANGES IN GROWTH PATTERNS, PUBERTY AND ADULT HEIGHT

The term secular trend has been used in growth research to describe changes over time in adult height, growth in children, changes in weight status/BMI and the timing of puberty. In order to be called a trend, the change should follow the same direction, usually for at least three measurements. Increases in adult height and height during childhood over time have been described as a positive secular trend; however, secular trends can also be negative, or absent; the latter being seen for adult height in some archeological studies (204). Secular changes are linked to changed living conditions, where nutrition, diseases, sanitation and socio-economic circumstances are of importance (4, 7, 189, 201, 205).

Secular changes in adult height

Broadly speaking, the last 150 years have been characterised by a general positive secular trend for adult height, with variations in the magnitude and exact timing of changes between countries and sexes. In Europe and the US, data on height in males is available from the last 150–250 years; most of these data come from measurements of military conscripts; in the US, data are also available from height measurements of slaves (both sexes). Looking at the available data as a whole, there was generally a positive secular trend in the late 18th century, which was followed in the early 19th century by either no trend or sometimes a negative trend. From the mid-to-late 19th century onwards, a positive trend was seen; this typically became most pronounced in the first half of the 20th century, by which time also female height was measured more routinely. Secular changes can also be studied in subsets of a population; the most common such studies being conducted in immigrants. Fischberg (1905) studied adult height in immigrant Jews living in New York and compared their stature with published data on Jews from Eastern Europe (201). He found that, on average, immigrants were taller than non-immigrants, and that second generation immigrants were taller than first generation immigrants. Since then, numerous studies have demonstrated positive secular trends in immigrants groups; demonstrating both secular changes per se and the plasticity in human growth; illustrating that growth is more than just the result of our genes (201).

A recent meta-analysis of height measurements from 200 countries worldwide investigated the secular change in adult height in cohorts born between 1896 and 1996 (Figure I.17) (206). In 1896, the shortest populations were in Asia and Central/Andean Latin America; females in Guatemala and males in Laos had mean heights of 140 and 150 cm, respectively.

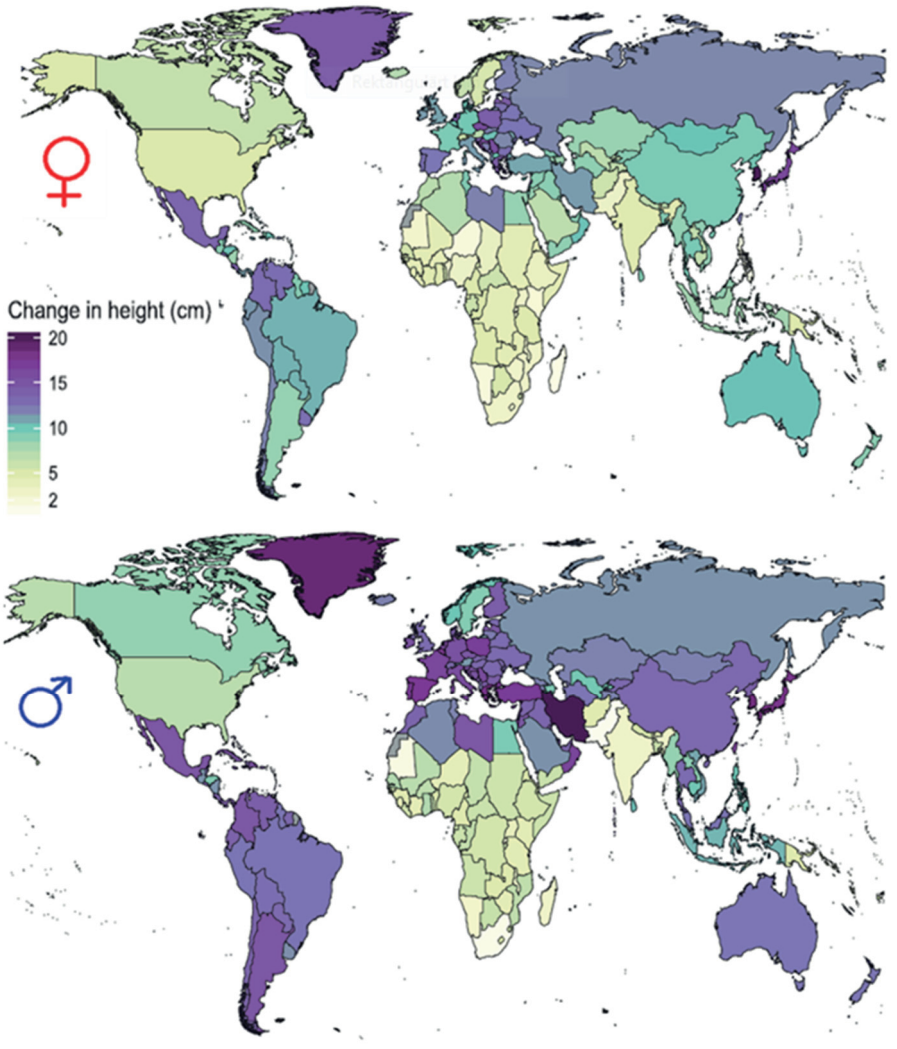


Figure I.16. Secular changes in adult height from 1896–1996. Change in mean adult height around the world. From Collaboration NCDRF (206).

The tallest populations at that time lived in Central/Northern Europe, North America and some Pacific islands. The tallest women lived in Sweden (160.3 cm), and women in Norway, Iceland, the US and American Samoa were similarly of tall stature; the tallest men lived in Sweden, Norway and the US (all above 171 cm). Between 1896 and 1996, the most pronounced positive secular trends occurred in South Korean women (20 cm taller during the 20th century) and Iranian men (16.5 cm taller during the 20th century). In many sub-Saharan countries and the Indian sub-continent, there was a weak positive secular trend during the first half of the 20th century for both sexes, followed by no trend or even a negative secular change in some African countries. In the US, the secular trend for both sexes was positive, but weaker than in Europe (206).

Dutch males increased in height from 165 cm to 184 cm from 1865 to 2000, men and women in the Netherlands are today the tallest in the world, with evidence that the trend now has stopped (206, 207). Some studies from other Northern European countries have also reported a levelling-off or stop of the trend around the late 20th /early 21st century (71, 208, 209). In the Nordic countries there have been an ongoing positive secular trend during the 20th century for both sexes, the Nordic populations are among the 10 tallest populations in both females and males (206, 210).

Secular changes during infancy and childhood

Adult height is the consequence of growth in utero, during infancy, childhood and puberty, thus; underlying changes in these growth periods may contribute differently to the secular changes in adult height. Even though length at birth correlates with adult height, changes in birth length are not generally considered to play a major role in secular changes in height. It is likely that increased growth during infancy is a factor that has contributed to positive secular trends in height during childhood, as well as in adult height, during the last century; however, long-term comparative studies in this age group are limited. There is, however, evidence of secular changes in height during childhood, principally based on record from school examinations/growth monitoring during the last 100–150 years (in Europe/ US/Japan).

In Europe, North America, Japan and South Korea there has been convincing evidence of a positive secular trend in childhood height during the 20th century (201, 204, 208, 211-224). In Japan, height at 6–12 years of age increased by 6–10

cm between 1920 and 1970, where reduced height was seen 1940-1950 (201). Height between 5 and 16 years of age was compared using a compilation of London school data (299 000 pupils) from 1905 to 1966; this analysis showed a clear trend for height to increase over time in both sexes. The trend was most pronounced from 1905 to 1938, and the author stated as to; "there being no positive trend after the 1959 survey"; however, the time interval between the last two surveys was only 7 years (225). Later UK studies have shown a continuous positive secular trend between 1960 and 1990 (215, 226, 227).

In Norway, positive secular trends in height have been documented for children born in the 1920s and more recently, with the most pronounced increases in height being between the cohorts born in 1920 and 1952 (228). The trend continued after 1952, with height during childhood becoming progressively greater (126, 228, 229). In Denmark, a positive secular trend in height in childhood was documented in publications from 1950 to 2014 (230-232). Finland has a long tradition of conducting large scale growth studies, which have documented positive secular trends in childhood growth from 1916 onwards (233).

The first large Swedish study of childhood growth was published in 1885; the author, Axel Key, aimed to develop growth references for height and weight between the ages of 7 and 21 years (234). The next Swedish growth reference from 1942, showed a marked increase in height during childhood, mean height increased by 3.7–7.5 cm for girls and 4.5–6.5 cm for boys (235). In a subsequent study, secular growth changes in schoolchildren in Stockholm born in 1933, 1943, 1953 and 1963 were studied, and height and weight at 7, 10 and 13 years of age, analysed. Increases in height at all time points were most pronounced when comparing children born in 1933 and 1943. Between 1943 and 1963 there was almost no increase in height at 7 years of age, a 1 cm/decade increase at 10 years of age and a 1–2 cm/decade increase at 13 years of age (213). Since then, there has been a positive secular trend for height during childhood, although not as pronounced as seen in Figure I17.

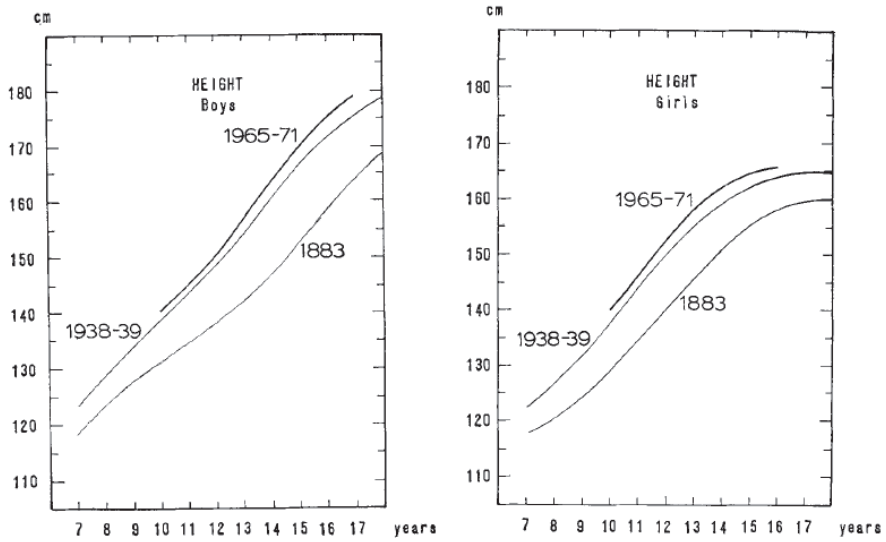


Figure I17. Secular changes in height during childhood and adolescence for Swedish girls and boys. Mean height in Swedish girls and boys measured in 1883 (Key, A), 1938–39 (Broman, B) and 1965–71 (Lindgren, G). Height in cm on the y-axis, age in years on the x-axis. From Ljung, BA (212).

Growth studies of immigrants (mainly performed in mid-20th century) have also shown positive secular changes in childhood growth (201). Japanese children in the US were more close to the mean height of American children of European ancestry than to the children of the same time in Japan (236). In Sweden, Neiderud has shown that second generation Greek immigrants (children born in Sweden) where significantly taller than age matched controls in Greece, with almost similar heights as Swedish children of Swedish born parents (237).

Secular changes associated with puberty

The timing of puberty also changes with time. Secular changes associated with puberty can be identified based on information about the development of sexual characteristics, age at menarche, age at voice-break and the timing of the pubertal growth spurt. Age at menarche has been studied extensively for more than a century, and studies show that age at menarche has fallen dramatically during the 20th century. In historic times, menarche was reported to occur at 12–14 years of age in India, Greece, Rome and China (350 BC to 600 AD). Both from medieval reports and estimation from skeletal samples, age at menarche was probably 12–15 years in Medieval Europe (900–550 AD) (238). In the Nordic countries and UK, data is available regarding

menarche from the early-mid 19th century, in France and Germany, data are available from late 19th century. In other European countries and the US, data are available from the beginning of 20th century, and from other parts of the world, data is in general available for the second half of the 20th century. Based on these data, age at menarche was 15–16 years in the 19th century, and 14–16 years around 1900. Since 1960, the trend for earlier menarche has levelled off, and many European countries today report mean age of menarche around or just below 13 years, with somewhat younger ages in the US and Asia (189). 12.5-13.05 in the Netherlands, 13.1 in Norway, 12.6 years in Italy 12.3 years in the US, 12.3 years in Japan, 12.2 years in Thailand and 12.4 years in China (189, 239-242). In Sweden, the mean age of menarche was 12.8 years in both girls born the late 1970s in Stockholm (243), and in a Gothenburg study of girls born 1978-1980 (244).

In males there is no general marker of pubertal timing; however, the change of voice – the voice-break – has received some attention as a defined event in mid-puberty. Voice-break for boys in the choirs managed by Johann Sebastian Bach (Leipzig 1732-1750) was recorded as being around 17 years of age. Studies from 1948–1976 reported voice-break at a mean of 13.2–13.9 years of age (201). In a longitudinal study of US adolescents born in the 1950s, mean age at voice-break was 13.5 years (3 month prior to PHV) (192). Males in the Swedish longitudinal studies of individuals born around 1956 from the Stockholm suburb of Solna ("Solna study") underwent voice-break at 13.9 years (PHV at 14.1 year) (157). A study of 463 Danish choir boys born in the 1980s found voice-break to occur 4 months earlier across the 10-year time period investigated, with most recent data showing a mean age at voice-break of 13.7 years (245). German boys born in late 1980s or early 1990s experienced voice-break at a mean age of 13.4 years (the same age as PHV) (246). Taken together, these studies imply a possible change for earlier voice-break over time in individuals with European ancestry.

In girls, a trend for an earlier onset of puberty has been observed during the 20th century based on the observation of earlier development of secondary sexual characteristics. As Tanner only defined the stages of puberty in the 1960s, limited comparisons can be made between present data and data from individuals born in the first half of the century. Despite this, it is highly likely that changes in menarche and growth patterns are related to the development

of secondary sex characteristics in some way. In the classic study outside London (Harpenden), mean age at B2 was 11.1 years; comparable values were reported in the Zurich longitudinal growth study (10.9 years) and the Solna study (11.0 years (152, 157, 247). American girls born in the 1950s (the same time period as the three European studies) had mean age at B2 of 11.2 years (192). In the 1990s, mean age at B2 was 10.7 years in the Netherlands, 10.0 years for girls in both Northern Italy and European Americans and 8.9 years for African–Americans (239, 248, 249). In another US study based on visits from 2004–2011 mean age at B2 was 8.8 years in African–American girls, and 9.7 years in girls of both European and Asian ancestry (250). In Denmark, there was a decline in age of thelarche from 10.9 to 9.9 years when examinations from 1991–1993 were compared with examinations from 2006–2008 (251).

For boys, there are few reports on the timing of development of secondary sexual characteristics. In longitudinal studies based on individuals born in the 1960s, mean age at G2 was 11.6 years in the study by Harpenden, 11.2 years in the Zurich study, 12.2 years in the Solna study, and 11.9 years in the US study by Lee (153, 157, 192, 252). Later studies reported mean age at G2 to be 11.6 years in Sweden, 11.5 years in the Netherlands, 11.2 years in Italy and 11.8 years in Denmark (249, 253-255). In Denmark, puberty (assessed based on testicular volume) was found to start 3 months earlier in examinations from 2006–2008 compared with examinations from 1991–1993 (256). In a large study of American boys born in late 1970s and in the 1980s, median age at G2 was 10.1 years in European Americans and 9.5 years in African–American boys. However, the early timing of G2 found in this study has been questioned (257). Due to the limited number of studies and variations in study design, it is not possible to confirm that there are general secular changes in the development of secondary sexual characteristics in boys, although it is likely to be the case.

In the 20th century, height during the adolescent years has shown a strong positive secular change in both sexes, suggesting an earlier onset of the pubertal transition. There are convincing studies in support of this finding from many European countries, the US, Japan and Korea (201, 208, 212, 216, 222, 224, 258-260).

Environment – can chemicals affect pubertal timing?

Pubertal transition is mediated by hormonal changes. There is evidence that certain compounds, labelled as endocrine-disrupting compounds (EDCs), can also influence pubertal development. EDCs are synthetic chemicals or natural compounds with the ability to interfere with endocrine signaling (261). The potential influence of EDCs was first noticed in the 1960s when Rachel Carson described the dramatic negative effects of pesticides on the health of coastal wildlife in her book Silent Spring (262). In humans, EDCs have been associated both with early and late onset of puberty. Causal relationships are difficult to prove when the exposure includes low doses of hundreds of chemicals since early in prenatal life. Additional difficulties when interpreting findings relate to the long latency between exposure in early life, and the observed potential consequences on pubertal timing some 8–15 years later. Taken together, the research field has identified sensitive periods during childhood during which the individual is more vulnerable or EDCs may be more toxic. In addition to timing of exposure, genetic susceptibility, dose, and duration of exposure may all modulate the effects of EDCs. Both animal experiments and human data have shown interactions between EDCs and pubertal onset, tempo, and age at menarche (261). To conclude; EDCs may in addition to an evolutionary perspective, and changes in earlier growth periods (see chapter 1.4 and 1.7) also be a factor for secular changes in pubertal timing (263).

1.6 THE GENETIC PARADOX AND PARENTAL INFLUENCE

Genes and weight/BMI

Obesity often runs in families; however, it is difficult to evaluate to what extent this observation is related to genes versus shared environment. Based on several studies, the proportion of variation in BMI explained by genes is estimated to be 45–80% (264). Genome-wide association (GWA) studies have become widely used in investigations of obesity and the genetics of human weight status during the last decade. GWA studies look at small sequences of genes (SNPs) on the whole genome, in order to identify associations between particular traits and variations in genes. GWA studies are hypothesis free and so, while they identify genes, the functions of the genes identified are typically explored in animal models. GWA studies have mapped more than a hundred genetic loci that are associated with BMI/adiposity; the genes identified together explain 3–4% of the total variation in adiposity (265).

Genes and puberty

The genetic contribution to variations in the age at menarche has been estimated to be 50–80% (266-269). In boys, there are less data on the relationship of genes to onset of puberty. However, the correlation between the onset of pubertal growth and PHV in identical male twins is above 90%, suggesting that genes play a major role (270). GWA studies in the last decade have mapped nearly 400 genetic loci associated with pubertal timing. The majority of these GWA analyses are based on women asked to recall retrospectively their age at menarche. However, studies have shown a large shared genetic aetiology of pubertal timing for girls and boys. To date, GWAs explain 7.4% of the variance in pubertal timing (271).

Genes and height

It has probably been known for hundreds of years that height in humans is heritable. This was first shown scientifically in the late 19th century by Sir Francis Galton (3, 190). Galton studied the relationship between the height of parents and children, and stated; "*when dealing with the transmission of stature from parents to children, the average height of the two parents is … all we need care to know about them"*. He proposed that children receive half their inherited characteristics from each parent and a quarter from each grandparent (190). Sir Ronald Fischer (creator of statistical science, credited with developing techniques such as the ANOVA and students-*t*-test and introducing p-value) calculated the first estimate of heritable height, identifying the proportion of total variation in height that could be explained by genetic variation. He hypothesised that variations in continuous variables such as height arise thanks to a combination of differences at many genetic loci which each have small effects (polygenic inheritance), a paradigm that remains scientifically relevant today.

Our current understanding regarding the hereditability of growth and adult height has been based largely on the findings of twin studies (272). From such studies it has been estimated that as much as 80% of the variation in height is inherited (273). Twin studies have also shown a high degree of concordance between identical twins in terms of growth patterns (272, 274). The possibility that the 80% value includes some non-genetic influences, owing to both common environmental and gene–environment interactions, cannot be excluded as the gene–environment interplay is very difficult to assess in practice (264). Studies in non-European populations have generally reported lower values for the degree of hereditability of stature; 65% of the variation in height has been reported to be inherited in men and women from western Africa and women in China (275, 276). It is not fully understood which general genetic differences between populations that influences height. People in southeastern Asia, and possibly eastern Asia, may have a somewhat smaller growth potential than people from other areas of the world; this difference may be owing to other biological, but non-genetic, intergenerational influences on growth (277).

Some evidence of genetic differences related to adult height between populations has been found. In the very short statured population of the Baka tribe in central Africa (Cameroon) under-expression of the GH receptor gene may explain the shortness (278). In European males, two different genes have been found with

significant correlations to attained adult height. Distribution of the Y haplogroup I-M170 gene in Europe is most common in South Western Scandinavia, the Northern part of the Netherlands and the Dinaric Alps, all regions with tall male stature. The Y haplogroup R1b-S116 gene is most common in Portugal, Spain, Southern France, Ireland and Scotland, countries/regions with shorter male stature compared to other Western European countries (209). From an evolutionary perspective, it is tempting to assume that the development of populations for hundreds of generations in widely separated environments, such as savannah, stubble, tundra, tropical rainforest and arctic, would have given rise to at least some biological differences. However, the rapid secular changes seen over the last 150 years indicate that the impact of genetic differences between populations may be more limited than heritability estimates in twin studies suggest.

In GWA studies, hundreds of thousands individuals have been genotyped and billions of gene variants across the genome have been analysed. Around 700 different gene variants have been found correlating with adult height. These known genes account for 16% of the variability in adult height (279). Taken together, genes identified by GWA studies of weight, pubertal timing, and adult height explain only 4–16% of the variation in these traits. This may be considered paradoxical, given the high estimates suggested for the heritability of weight, pubertal timing and height.

Look at the parents

Without knowing anything about genes, information on parental height is still an important factor for evaluating growth in children. Building on the studies of Galton and Fisher, Jim Tanner suggested mid-parental height as a measure that was informative regarding the final height of an individual in a presentation at an international pediatric congress in 1968, and later in a publication (98). The measure of mid-parental height was developed based on data from the growth studies conducted in London (Harpenden), Stockholm (Solna) and Zurich (98, 188, 280). Analysis showed that the height of the child was influenced equally by the height of each parent, so a measure of mean parental height was appropriate. However, because men are on average about 13 cm taller than women, one has to correct for the sex of the child when calculating the mid parental height (MPH) as seen in Figure I.31. More recent research has shown that modifications to the formula are needed in cases where the height of the parents differs from the mean height of the general; Tanner's formula is still used by pediatricians however, have

been improved, by taking different relations regarding stature and sex into account, being incorporated in Swedish references/charts (82, 83, 98, 101, 214, 281).

Correlations between the growth patterns of children from birth to adult height and those of their parents are largely unexplored. There is some evidence to suggest that growth patterns are hereditary based on twin studies (272, 282), as well as examinations of individuals with early or late onset of puberty (283, 284). Children referred to pediatric endocrinology clinics due to both early and late onset of puberty often have relatives who have a similar history of growth patterns (283, 284). Studies of the relationship of growth patterns between generations at a population level is largely absent, although a Danish study in a community based setting showed correlations between the timing of puberty, (based on secondary sex characteristics and menarche) in children and their parents (285) .

1.7 DOES WEIGHT INFLUENCE HEIGHT GAIN AND PUBERTAL TIMING?

Weight and BMI

Since growth monitoring started in the 19th century, it has been clear that weight and height in children are interdependent. From this time, tables showing weight alongside the corresponding height have been used in the evaluation of childhood growth. The *weight for height* concept has been used for more than 100 years in the assessment of whether a child is well nourished. BMI, weight in kilograms divided by the square of height in meters (kg/m^2), was introduced in 1871 by the Belgian statistician/auxologist Adolphe Quetelet, as a measure of body composition, and was originally known as Quatelet's index (3). It took 100 years before BMI was used as a measure of weight status in adults, and later on in childhood (286). It is important to note that BMI cannot differentiate how different tissues (muscles, adipose tissue (fat) and bones) contribute to body weight. Weight is correlated with body fat and also with height; however, height has only a weak correlation with body fat (287). BMI correlates with fat mass in children, and has become the most common proxy during the last 2–3 decades for defining whether a child or adolescent is thin, normal weight, overweight or obese (288). In normal-weight children, the correlation between BMI and fat tissue is less strong than in obese children (289). Weight, weight for height and BMI during childhood and puberty are, however, dependent on age; while growth curves for height and weight increase with age, BMI rises, then falls before rising again (Figure I.18).

As seen in Figure I.18, BMI is far from optimal; the more complicated weight-for-height indices giving less age dependent values, have however neither been used clinically nor frequently in research (290). Instead, BMI charts have been published showing values during childhood and puberty corresponding to being overweight (BMI above 25) or obese (BMI above 30); these were later supplemented with charts showing thinness based on the WHO adult cut-offs of 18.5, 17, and 16 kg/m^2 (291-293). To summarise; in infancy, BMI is not a valid measure of body composition, and during puberty, the association between body fat and BMI is weaker than during childhood or adulthood (Figure I.19) (290).

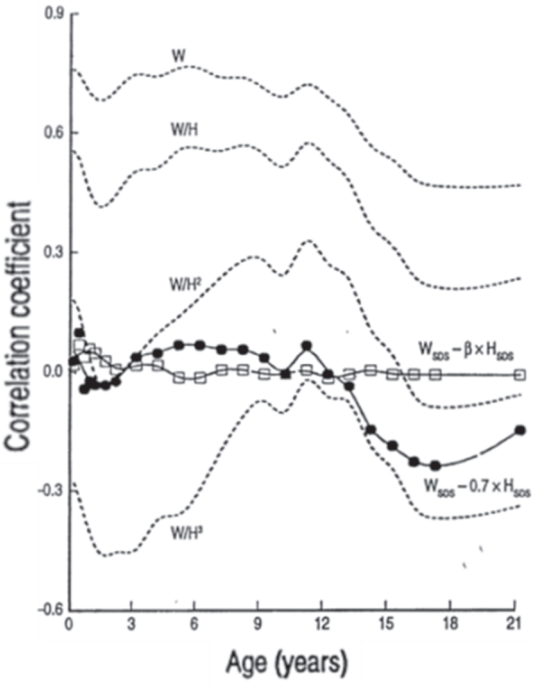


Figure I.18. Weight for height indices. The age dependent pattern in the correlation coefficients of weight-for-height indices related to height is shown in girls. From top to bottom for; weight (W), weight for height (W/H), weight for height^2 (W/H^2), and weight for height^3 (W/H^3). Two additional weight-for-height indices are adjusting weight$_{SDS}$ for height$_{SDS}$ with a linear regression giving residuals (weight$_{SDS}$ – *β* x height$_{SDS}$) for regression weight *β*. The age independent weight-for-height index (weight$_{SDS}$ –0.7 x height$_{SDS}$), approximating *β* over all ages and both sexes with common value of 0.7, has almost no correlation with height until 13 years of age. The age dependent weight-for-height index (weight$_{SDS}$ – *β* x height$_{SDS}$) has an optimal age specific *β* value for each age interval, and has almost no correlation with height over the whole age range. This means that the last two weight for height indices are more appropriate for evaluating weight status during infancy, childhood and adolescence than the indices, mainly used today; W, W/H,W/H^2,W/H^{3}l. From Karlberg J and Albertsson-Wikland K (290).

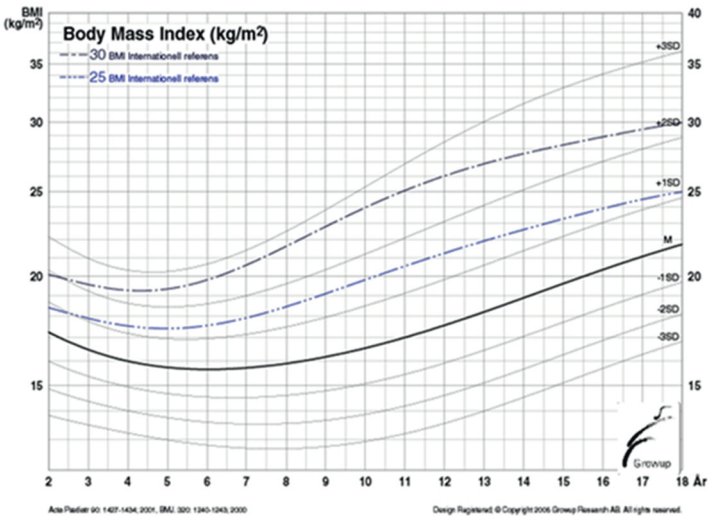


Figure I19. Body mass index (BMI) chart for use during childhood and puberty. Mean BMI reference values are shown alongside SDS lines. Dashed lines represent the international obesity tasks force (IOTF) cut off values used to define being overweight (BMI equivalent to 25 kg/m^2) and obese (30 kg/m^2) (291). From Karlberg, J et al (294).

At birth

Already in the 1920s, it was found that a high birth weight was associated with later childhood obesity (295). Since then, many studies have tracked childhood obesity back to birth, noting a significantly higher prevalence of obesity in infants starting life with a high birth weight compared to those with an average birth weight (296-298). Many studies have also shown that a high birth weight correlates with taller height during childhood and a greater attained adult height. Since weight and height at birth are highly correlated, and there are associations between size at birth and later stature (despite the tendency for adaptation to mid-parental height during infancy), is it hard to distinguish the specific impact of birth weight on subsequent height gain. Size at birth may also influence the timing of pubertal growth; however, the findings are complex and the relationship appears to be non-linear. Infants of both sexes who are born large for gestational age (LGA) start pubertal growth earlier than their normal-weight counterparts, and experience a pubertal growth spurt of longer duration (299). Previous studies have also found that children born SGA are more likely to enter puberty early compared with their normal-weight peers (300, 301). These findings are consistent with a U-shaped relationship between length/weight at birth and puberty; both extremes in the normal distribution of length/weight at birth are associated with earlier puberty.

Infancy/failure to thrive

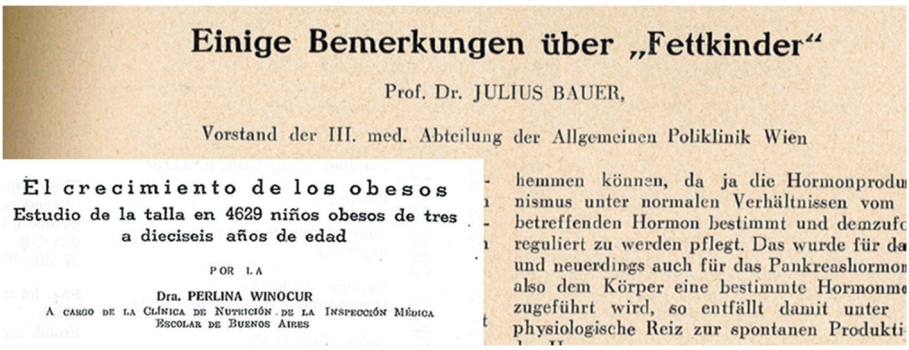
Rapid weight gain in infancy is associated with accelerated linear growth. Conversely, poor weight gain in infancy is a common cause of growth failure during the first year of life. Major causes of stunted growth worldwide are insufficient nutrition, repeated acute infections and chronic infections in infancy (302). Even in affluent countries FTT, with little weight gain in infancy, is an important factor for subsequent height gain (9). FTT was described more than 100 years ago as a condition of malnutrition in infants, associated with inadequate weight gain. Later, the term was used to describe various kinds of deviations in growth in infancy, irrespective of the presence of underlying disease. Unfortunately, later, the term has been used to describe various kinds of deviations in growth in infancy, irrespective of the presence of underlying disease. There are different definitions of FTT; the definition of FTT should preferably identify children with slow/weak/absent weight gain, and not infants who are constitutionally small, i.e. following its growth channel according to the size of their short parents. This means that two or

more measurements over time are needed to define FTT. Catch up in weight during the first year of life can be followed by catch up in height. If there is no catch up in weight, it may affect further height gain and even adult height (9, 10, 12).

There is evidence indicating that catch up growth in height is dependent on both adequate nutrition and good psycho-social circumstances. For example, the pattern of catch up/height gain was very different in orphans compared to children living with their parents after World War I. Orphans remained stunted; although they gained weight after peace they did not gain height, whereas children living with parents caught up in height (303). In an affluent society, children with FTT without an underlying medical diagnosis, in particular, are at risk of impaired gain in height later in childhood, indicating that psycho-social factors are important (9).

Overweight, obesity and childhood growth

From the 1920s to1940s it was noted from studies in Germany, France, the UK, Argentina, Sweden and Canada, that obese children were generally taller than normal-weight children, and that being overweight/obese (ow/ob) during childhood was associated with increased height velocity (304), (305-307).



Einige Bemerkungen über „Fettkinder"

Prof. Dr. JULIUS BAUER,

Vorstand der III. med. Abteilung der Allgemeinen Poliklinik Wien

hemmen können, da ja die Hormonprodu
nismus unter normalen Verhältnissen vom
betreffenden Hormon bestimmt und demzufo
reguliert zu werden pflegt. Das wurde für da
und neuerdings auch für das Pankreashormo
also dem Körper eine bestimmte Hormonme
zugeführt wird, so entfällt damit unter
physiologische Reiz zur spontanen Produkti

El crecimiento de los obesos

Estudio de la talla en 4629 niños obesos de tres a dieciseis años de edad

POR LA

Dra. PERLINA WINOCUR

A CARGO DE LA CLÍNICA DE NUTRICIÓN DE LA INSPECCIÓN MÉDICA ESCOLAR DE BUENOS AIRES

Figure I.20. Original publication titles concerning obesity and childhood growth. From Bauer, J (295) and Winocur, P (307).

De-Simone et al. found that ow/ob children were taller than normal-weight controls up to the age of 12.5–13 years (308). In the Swedish growth cohort born in 1974, children whose BMI increased from 2 to 8 years, were taller at 8 years of age than children whose BMI had not increased (309). Some of the secular trend for taller stature during childhood can be explained by increased

BMI/weight, as seen in a large Danish study (310). However, another study did not find correlations between BMI and the secular trend for taller height. In studies of individuals born in Sweden from 1933 to 1963, there was a significant increase in height at 7–13 years of age without an increase in BMI/weight for age (213).

Overweight, obesity and puberty

In the 17th century, the English midwife Jane Sharp, stated in a text for midwives; *"Generally maids have their terms at about fourteen years old...and plenty of nutrient brings them down sometimes at twelve years"*. Similar ideas have also been expressed in medical texts from physicians in Germany and Italy in the 17–18th centuries (3). Since the early 1930s, and with numerous reports thereafter, there has been an association between obesity and early puberty in girls; for boys, the results are more ambiguous. In 1901, Frölich led the pediatric/endocrine society into the assumption that obesity in boys was associated with late or even deficient pubertal development (311). In 1948, Mossberg found early puberty in obese boys in Sweden; a finding confirmed by Wolff in the UK in 1955 (312, 313). In 1974, Frisch and McArthur published the "critical mass theory" in Science, stating that the onset of female puberty is dependent on having a certain amount of body fat (314).

Many of the previous studies showing relationships between higher weight status during childhood and taller height mentioned above also found correlations between increased weight in childhood and early puberty. In the Swedish growth cohort born in 1974, a greater BMI gain from 2 to 8 years of age was related to an earlier onset of puberty; this study was conducted in a population just before the obesity epidemic (309). The American NHANES studies found that obesity was associated with early puberty in girls. For boys, early puberty was instead associated with a low BMI (315). In Denmark, studies have found that both girls and boys with higher than average BMI had earlier pubertal growth than children with BMI below the median (310). The same trend was seen in the Dutch cross-sectional study which took measurements from 1955 to 1997 (222). In a Spanish study, there was a positive relationship between age at onset of puberty and BMI in childhood for boys, but not girls (316). This study also found a correlation between subcutaneous adipose tissue (skinfold) and onset of puberty for both

sexes. A Danish study of choirboys found a correlation between BMI at 8 years of age and earlier voice-break (245). Mean age at voice-break was 12.8 years for overweight/obese boys, 13.4 years for boys of average weight and 14.5 years for thin boys. In contrast to results from multiple European, Japanese and Chinese studies (254, 308, 310, 312, 313, 317-319), US-based studies have in general shown an association between obesity and late puberty in boys (315, 320)

Eating disorders and medication affecting appetite

Eating disorders are prevalent during the adolescent years, especially in girls (321). Eating disorders are characterised by irregular eating habits and severe distress or concern about body weight or shape. Anorexia nervosa (AN) is the most serious and best-studied disorder; it is accompanied by an obsessive fear of weight gain, refusal to retain/maintain a healthy body weight and an unrealistic negative perception of body image. In AN, if the condition begins before adult height is reached, weight loss is followed by impaired height gain. Girls presenting with AN starting before menarche are at risk of impaired height gain by undernutrition. The growth pattern in early puberty for girls with AN may be hard to distinguish from the normal pattern of slow growth seen before the onset of the pubertal growth spurt. AN also affects pubertal maturation; development does not proceed as normally expected. With adequate treatment resulting in weight gain, girls with AN gain height and catch up growth is possible, although adult height may be affected (321).

For the last few decades, stimulant drugs have been widely used in late childhood and during the adolescent years due to attention-deficit hyperactivity disorder. Stimulant medications are often associated with changes in appetite (usually decreased appetite), risk of weight loss and a subsequent risk of impaired height gain (322, 323). Titrating the dose to the therapeutic response (or reconsidering the use of the drug) together with careful monitoring of growth is therefore essential.

1.8 MEASUREMENTS, GROWTH REFERENCES & MODELLING

How to measure length/height and weight

To make reliable assessments of growth, there is a need for standardised equipment and techniques that allow measurement to be reproduced independently of who is measuring the infant, child or adolescent. In affluent countries, infants are typically weighed naked at maternity wards and well-baby clinics (WBC) using special baby scales; in other parts of the world, the baby may sometimes be weighed together with the mother. Weight at birth is generally rounded to the nearest 10 grams. During infancy, weight may be recorded on growth charts to the closest 10, 50 or 100 grams. Height is measured by the infant in a supine position, as shown in Figure I.21 (324). Infants are sometimes also measured using a measuring-tape; this is likely to increase variations between measurements/measurers, and not recommended.

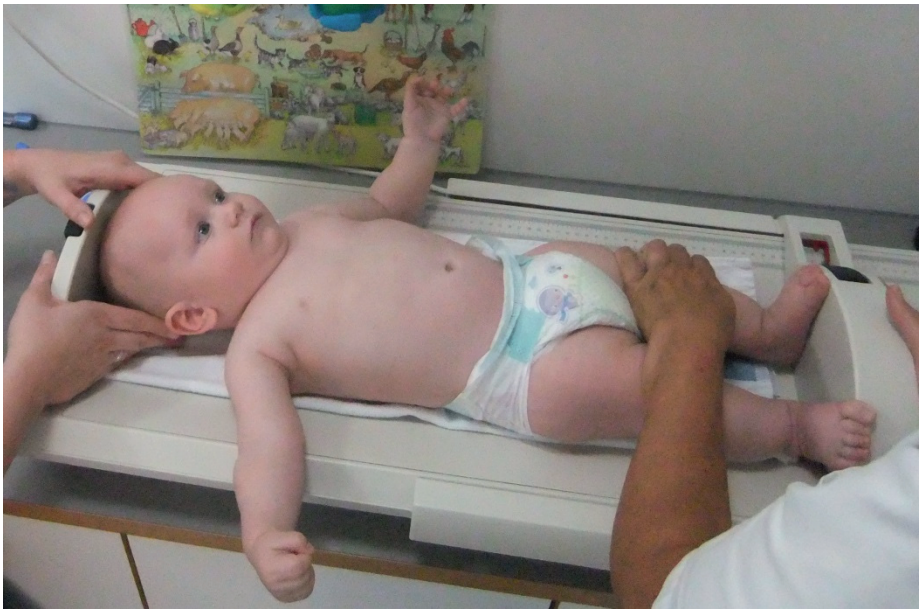


Figure I.21. How to measure length of an infant. Length is measured by the infant in a supine position on a special length board; the infant should be lying straight, with legs in full contact with the board and feet at a 90 degree angle. Length is noted to the closest mm. The assistance of a parent/caretaker may be needed to ensure that the knees do not bend and the heels remain down. Photo from the Department of Pediatrics, Halmstad, Halland Hospital, Sweden.

From 2 years of life onwards, it is recommended to measure standing height instead of length; standing height is, on average, 0.75 cm less than supine length (0.6-1.0 cm in different studies) (80, 188). When the infant/child is standing, weight measurements can be made using ordinary scales, either naked or in underwear/dry diaper. Weight is typically recorded to the closest 100 grams. Height should be measured with the child/adolescent standing with their back against a wall or against the back of a stadiometer (Figure I.22) (325). With increasing age, children/adolescents are often measured in light indoor clothes.

Figure I.22. How to measure height in a child or adolescent. Height should be measured with the child/adolescent standing with their back against a wall or against the back of a stadiometer/measuring instrument; feet should be flat on the floor, and the legs and back straight. Heels, buttocks, and shoulder blades should be adjacent to the wall/stadiometer. The head should be in the correct plan; eyes looking straight ahead or very slightly downwards, with the upper border of the eye socket parallel with the upper boarder of the ear (current Swedish recommendations). In some guidelines it is recommended that the child should stretch up with and a slight upward pressure is applied behind the ear and with the child´s head adjusted to achieve a horizontal " Frankfurt plane ". The headboard on the wall/stadiometer is then lowered until it makes good contact with the head, and then height is measured. Height is recorded on a growth chart; at the precise value in millimeters. The measuring equipment should be calibrated regularly. Photo from the Department of Pediatrics, Halmstad, Halland Hospital, Sweden.

Other measures of growth, body composition and maturation

In infancy, measurements of head circumference are important for detecting deviations in development. For this reason, references for head circumference have been developed alongside those for height and weight (Figure I.31). Waist circumference (WC) is becoming a more commonly used measurement of body composition, as it gives an estimate of abdominal fat mass and serves as a proxy for obesity (326, 327). Conversely, scapular fold measurement to assess thinness is not commonly used today in children, particularly in more affluent countries. Since the 1990s, more sophisticated measurements of body composition can be made using 3-D photonic body scanning, although their use in children is currently limited (328, 329).

Radiographic methods are theoretically of use in auxology; however, they are of limited use in clinical practice partly due to complexity and radioactivity, but also to the fact that X-rays and CT-scans (computed tomography) measure supine length rather than standing height. In special circumstances, X-ray may be used with radiolucent implants when following bone growth after, for example, growth reducing surgery (epiphysiodesis) in adolescents with predicted extreme tall adult height and to monitor growth in Crohn's disease (19, 330, 331). In such cases, the growth of the long bones (femur or fibula) is followed in detail. In clinical radiology bone length measurements is standard in cases of unequal bone length.

Magnetic resonance imaging (MRI) has been used increasingly in pediatric/adolescent research studies for auxological purposes during the last decade. MRI has the advantage over other methods of not using gamma radiation (radioactivity); however, it is time consuming, expensive and measures laying length. It does have the advantage of measuring body fat. Body-fat/body composition can also be measured by dual-energy X-ray absorptiometry (DXA). DXA use very low level of radiation and gives information on body composition by calculating fat mass, lean soft tissue and bone mineral content in adults as well as in children and adolescents (332). Thus, DXA can differentiate between muscles (included in lean soft tissue) and fat mass (333). DXA can separate longitudinal bone growth from bone acquisition (334). Although the potential for errors (variation between different measurers) when measuring WC is greater than for height and weight, results are typically reproducible and correlate with total body fat and central adiposity when compared to DXA (333).

For detailed measurements of short-term growth, knemometers have been used (Figure I.7). This is a special chair with a technical device for measuring the lower leg, and is used in children and adolescents to measure the distance between the knee and heel (130). Knemometric measurements show a measurement error of less than 160 µm (0.16 mm). A portable mini-knemometer is available for use in infancy and during the first year of childhood, described by Michaelsen (335). Knemometric studies have been valuable in neonatal growth research for evaluating short-term growth, including seasonal variations; however, they are not used in clinical growth monitoring (see chapter 1.2).

During the adolescent years, the pubertal maturation is of importance when evaluating the growth/development of a juvenile/adolescent. The assessment is generally performed by stages according to Tanner in both sexes and with the orchidometer in boys (152, 153, 156, 158) (Figure I.10). Self-assessment of pubertal maturation have been validated in several studies, in general less accurate than evaluation by a skilled professional, however sometimes an alternative (better than not assessing maturation at all) (336, 337). The maturation during both childhood and puberty has since the 1950s been evaluated by X-ray of the (non-dominant) hand and wrist, since there is a correlation of the maturity of bones in the hand and the long bones (338). The first reference of 1952 in US, Greulich and Pyle, was followed by an European method and they are is still in use (339). An estimation of bone age (BA) is indicated for assessment and treatment of growth disorders and prediction of height in some clinical situations (see chapter 1.9).

Growth references and standards

Growth references or standards show the mean/median and distribution of an anthropometric measure, separate for each sex, related to age in a group of children. Many biological traits and auxological measures vary within a normal distribution. The Gaussian curve (after the German mathematician Carl Friedrich Gauss), illustrates how variations in height or other variables within a population are normally distributed as seen in Figures I.23 and I.24.

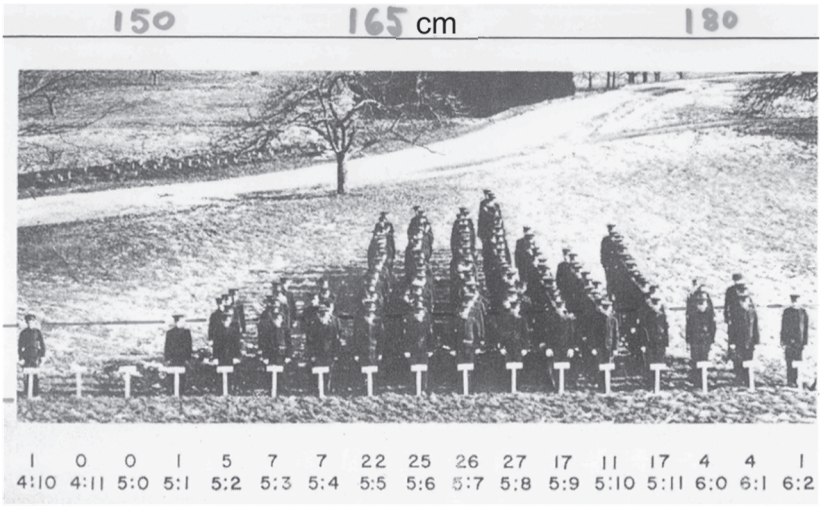


Figure I.23. Students at Connecticut agricultural college, approx., year 1900.

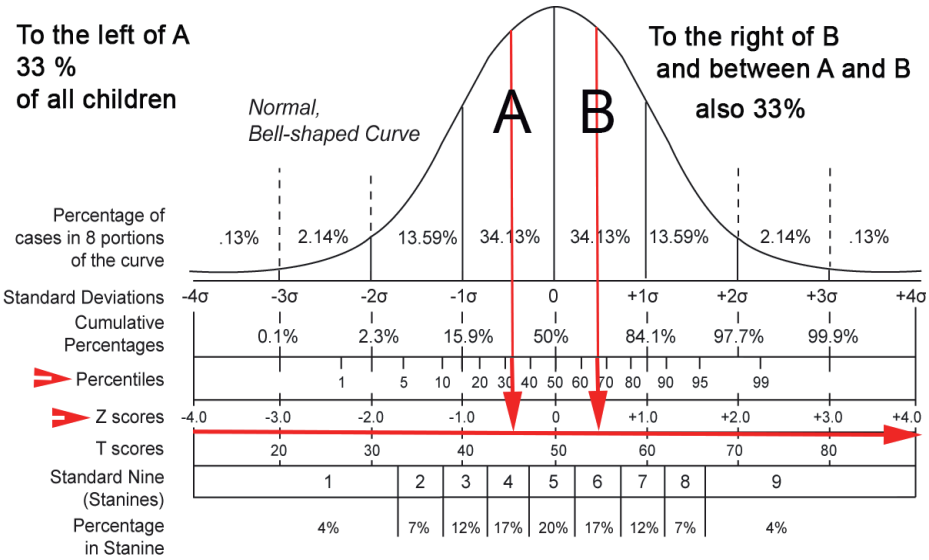


Figure I.24. The bell-shaped curve for normal distribution The Gaussian curve showing the normal distribution.

Height is often normally distributed outside the adolescent years; however, weight typically has a skewed distribution during this time period. References, most commonly are developed for height and weight. Growth references/standards are essential for the assessment and monitoring of growth. Due to variations in growth patterns between populations and over

time, most researchers recommend that growth references are preferably country/population-specific and should be updated regularly; however, the WHO has argued for the general use of a multiethnic growth reference published in 2006-2007 (340, 341).

Growth reference or growth standard?

Growth references are in theory constructed based on data from a representative sample of the target population, and growth standards are constructed from a group of children from the target population who can be assumed to be growing optimally (342). The difference between references and standards is, therefore, dependent on inclusion and exclusion criteria. During the last few decades, however; most references in practice can be classed as growth standards because of the exclusion of children with diseases and/or malformations, as well as those who were born prematurely or with a low birth weight.

The WHO growth standards (for children aged 0–5 years) were based on data from infants from families in favorable socio-economic conditions, who were breastfed and had non-smoking mothers, aiming for optimised growth (341, 343). Despite this, there are significant differences between the WHO standard and national references; despite the terminology, national references in European countries show greater heights during the childhood years than represented in the WHO standard, questioning the use of this standard in Europe (344-347). If the WHO growth standards are used in European countries, many children of short stature would be classified as having normal stature. For tall children and children with above average head circumference (in taller than average populations) the WHO growth reference may also lead to inappropriate concerns that the height or head circumference is pathologically high (348). In a low income country as Nigeria, there is a risk to under-diagnose under-weight when using the WHO growth standard (349). Due to the increasing worldwide trend for children to be overweight or obese, weight standards in which the very thin and obese have been excluded, are also preferable when constructing a weight standard.

Cross-sectional or longitudinal studies?

Many of the classic studies that contributed to the knowledge of human growth were longitudinal studies, in which every child was followed and measured repeatedly. The alternative way of studying growth is in cross-sectional or semi-cross-sectional studies, in which individuals are measured once, or on a few occasions, respectively. Although it is impossible to study individual growth patterns without longitudinal studies, there is a role for cross-sectional studies. Several references today were developed from studies of cross-sectional data. The results were comparable with those obtained from longitudinal studies in terms of mean height and weight values. Studies using cross-sectional data are, however, unable to estimate PHV correctly, as exemplified in Figures I.14 and I.25. The "Merrell bias" in the population curve, described by Margaret Merrell in 1931, shows how cross-sectional studies underestimate PHV (350). This is due to the broad variation in pubertal timing. It can be concluded, therefore, that longitudinal data are needed to quantify the pubertal growth spurt correctly. Longitudinal studies are also essential to get insight into factors affecting human growth.

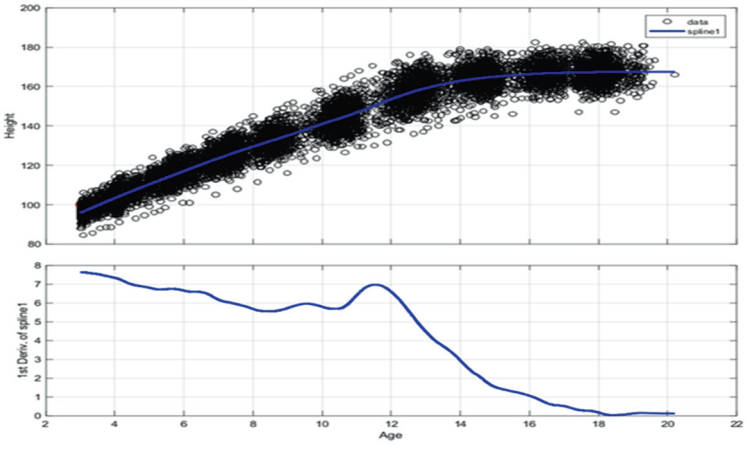


Figure I.25. Cross-sectional data cannot be used to estimate mean individual peak height velocity (PHV). Height and height velocity of girls in the Grow Up 1974 Gothenburg population are shown. Due to variations in the timing of pubertal growth, PHV is blunted (compared to individual curves in Figure I.14) and is therefore not representative of mean individual PHV. Longitudinal data, however; mathematically treated as cross-sectional are used for this figure.

Why model human growth ?

Growth models are useful both for describing and understanding human growth (Figure I.1). A model can be used in order to test hypotheses regarding the regulation of growth, in particular, those relating to the

physiological mechanisms that underlie the different phases of growth in humans (1). With a growth model it is also possible to predict future height gain.

Different growth models

Mathematical descriptions of growth in the first half of the 20th century focused on identifying common patterns among different species (including humans) by modification of a general S-shaped growth curve spanning from the start to the end of organic growth (351). These models worked well for many organisms, but failed to model human growth adequately owing to the characteristics of both the infancy and pubertal growth periods. In the 1940s, the Swedish professor of anatomy Gaston Backman described human growth as three different biological periods, linked to mathematical functions (352, 353). The first period was from fetal life until approximately 3 years age, followed by period of basic growth ("*grundwachstums*" in German) from approximately 3 until 25 years of age, and then a superimposed pubertal growth function from 13 to 20 years of age (Figure I.26).

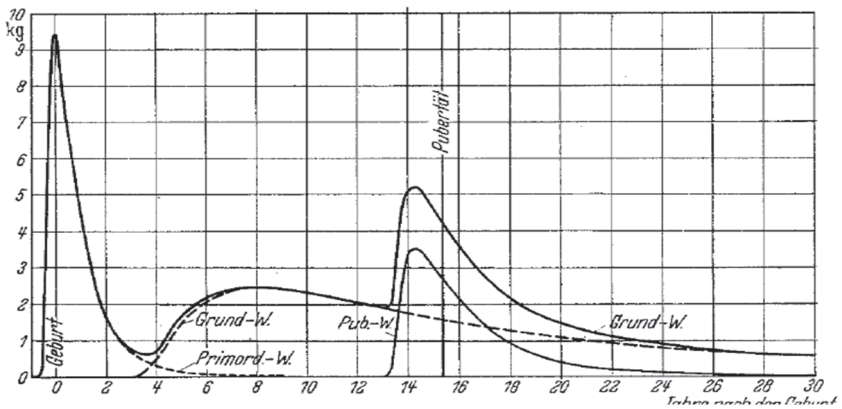


Fig I26. Backman's description of human growth. The Swedish professor of anatomy published papers and books in the 1920s to 1940s showing that human growth was composed from three mathematical growth functions. This figure shows weight velocity; the x-axis shows age in years, the y-axis shows weight in kilograms. *Geburt* means birth, *Primordial wachst* is similar to fetal/infancy growth, *Grund wachst* resembles childhood/continuous growth and *Pubertät* equals pubertal growth. From Backman, G (353).

Several different mathematical models have been developed for modelling human growth during the last 50 years. Most model growth from early childhood until adult height, or near adult height (351, 354-357). A separate

group of models have been dealing with the challenge of describing individual growth patterns during puberty. The Preece-Baines (PB1) model, which has been widely used to construct growth charts, can be used to model growth during puberty, but has limited precision when modelling growth during the first 1.5–2 years of life (356). In a study of three different growth models; PB1, Jolicoeur-Pontier-Pernin-Sempé (JPPS) and Shohoji-Sasaki modified by Cole (SSC), the JJPS model was found to be superior to the other two when the modelled height was compared to actual measurements (357). The JJPS model also had a slight peak during childhood suggesting a mid-growth spurt.

ICP

The ICP model was developed by Karlberg et al. in the 1980s (358-361), and also adapted for girls with Turners (362). The model was developed from the height velocity curves of 157 individuals included in the population on which the former Swedish growth standard was based (157). In the model, growth is divided into three additive, partly superimposed components representing infancy, childhood, and puberty (ICP). ICP is a mathematical model in which an exponential infancy component, a quadratic childhood component and a sigmoid puberty component, describe human growth from late-intrauterine life to adult height. The total growth during puberty is the sum of the C and the P components, pubertal growth can be individualised, depending on the C component, with a fixed P component (Figure I.27).

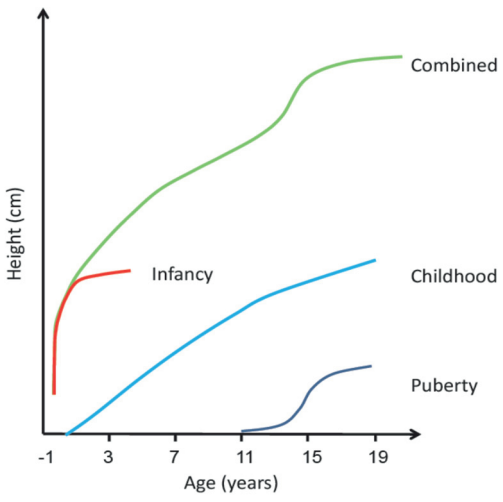


Figure I.27. The ICP model. The different components of the infancy–childhood–puberty (ICP) growth model are shown individually according to age. From Albin, AK (363) modified by permission of original publication Karlberg, J.,(359).

SITAR

The first published model to allow adjustment to take into account individual differences in the timing, tempo and magnitude of the pubertal growth spurt was the SITAR-model (Super-Imposed by Translation and Rotation) (364). SITAR follows the same principles as the shape-invariant model proposed by Beath that was originally used to model weight in infancy (355). A single, fitted curve is constructed that is modified by the inclusion of three parameters; shifting the curve vertically for size/amplitude, horizontally for onset, and shrinking–stretching horizontally for tempo/velocity. Although the model can be modified to include growth during infancy, it has not been extended to describe growth all the way from birth to adult height (224, 365).

QEPS

Working with the pre pubertal growth in two mathematical models for prediction of GH dependent growth, it was empirically found that the model for spontaneous pre pubertal growth, (QE-functions), could be generalised to the entire period from early life to adult height when incorporating also the pubertal growth phase, resulting in the full QEPS model (366-368). Thereafter, the full model, including also the pubertal growth was developed, describing human growth from fetal life to adult height (Figure I.28). The format of the model was inspired by the ICP model; both models use mathematical functions to describe phases of growth. The QEPS model describes growth from foetus to adult height using four mathematical functions. Height gain is described as a sum of the growth functions; Quadratic (*Q*), exponential (*E*), pubertal (*P*), and stopping (*S*). Basic information on the QEPS model has been presented at scientific meetings (369, 370), and the peer-reviewed scientific publication describing the model is attached as an appendix to this thesis.

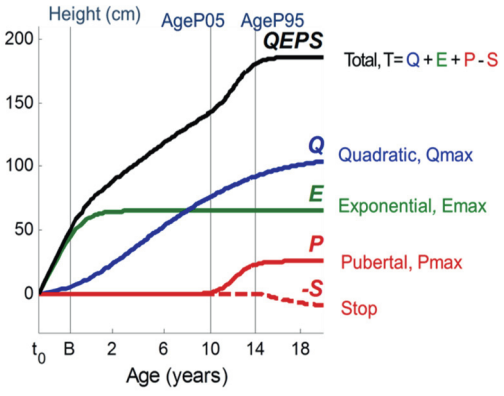


Figure I.28. The QEPS model. Basic figure of QEPS. Total height is the sum of four growth functions: Quadratic (Q), Exponential (E), Pubertal (P), and Stop (S). B = birth, t0 = about 6 weeks after conception. The vertical lines indicate birth, and the onset (AgeP5) and end (AgeP95) of the pubertal growth.

How to describe & model pubertal growth?

As mentioned earlier, the years preceding puberty are generally characterised by slowly declining height velocity (371, 372). It has been challenging to describe and model variations in the timing of pubertal growth, as well as the S-shaped pattern of growth during the pubertal years.

The onset of the pubertal growth spurt can be identified based on the lowest height velocity preceding the spurt; this is often referred to as the take-off, onset, nadir or insertion point (260, 372, 373). In the ICP model and some other studies, it has also been defined as the point where height has increased by 0.3 SD-scores from the pre pubertal curve, or as the point 2 years before peak height velocity (PHV) (188, 371, 374). The distribution of height during the pubertal years becomes skewed, as observed by Frank Boas in the 1880-1890s (375, 376) and analysed later in more detail by Merrell (350). Based on a detailed study involving visual inspection of individual growth curves during puberty, Taranger and Hägg proposed several measures of pubertal growth (Figure I.29). They defined three measures of the beginning of pubertal growth (186).

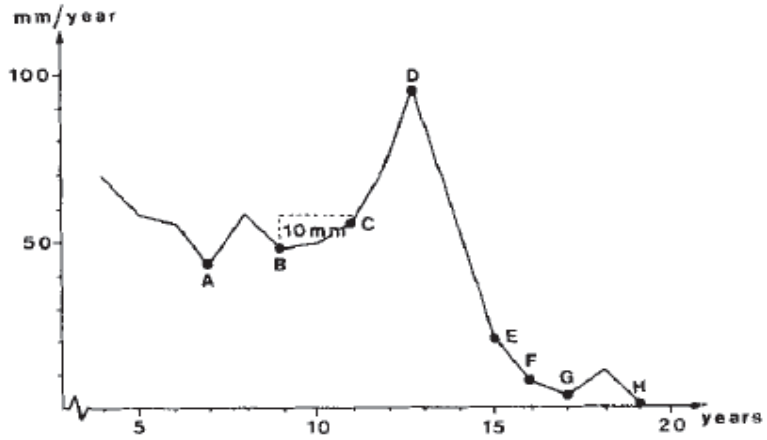


Figure I.29. Taranger and Häggs definitions of pubertal growth. Measures for different parts of the pubertal growth. For onset of puberty; *A. Minimum*; age at the lowest height velocity before PHV, *B. Start*;age at the point from which there was a continuous increase in height velocity and *C Onset*; age at the point where growth rate has increased by10 mm since start. For mid puberty; *D. PHV*. For end of puberty; *E. D-20, F. D-10,* and *G. D5* were defined. D stands for deceleration, and the values indicate the height velocity; hence, D20 is the point where height velocity has decelerated to 20 mm/year with consistent definitions for D-10 and D-5. *H. D-zero* is the first of three consecutive annual increments each being below 5 mm. From Taranger, J and Hägg, U (186).

PHV represents the point at which growth during puberty is most pronounced; occurring in *mid-puberty*. Numerous studies have used PHV as the only estimate of pubertal growth. PHV can be estimated in different ways. The easiest (and probably most unreliable) way of defining age at PHV is by estimating the age when height increases most based on visual inspection of the growth curve. Assessments made based on visual inspection can be improved when supported by a special ruler (Figure I.30) (377).

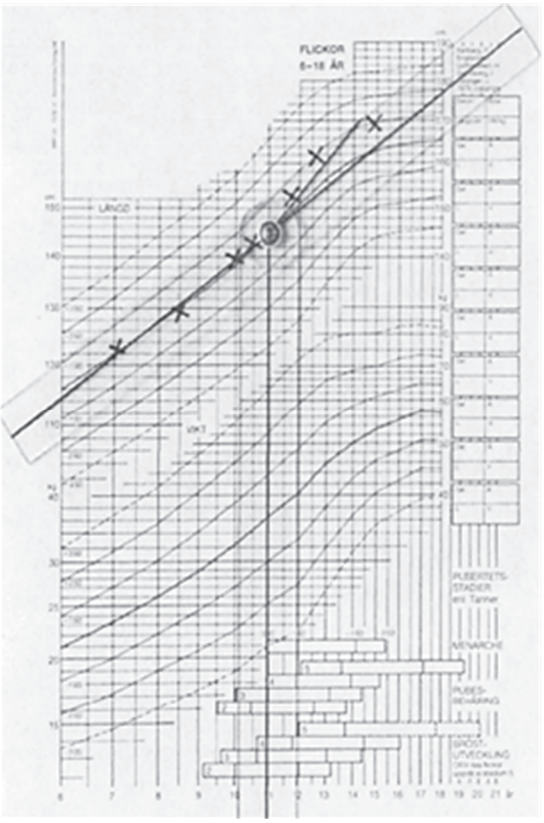


Figure I.30. Special ruler used to estimate onset of pubertal growth. The left angle of the ruler is aligned with the assumed pre-pubertal height values, and the right angle of the ruler with the pubertal growth spurt values. The long vertical ruler indicates the child's estimated age at the onset of the pubertal growth spurt From Person I, et al. (377).

Age at PHV may also be determined by visual inspection of the change in height velocity displayed in a computer-generated height velocity chart (260, 378). Another way of defining age at PHV is to calculate the midpoint between the two measurements that are separate by the greatest height . This method is reliable when height measurements are available every 3 months, but is less precise when measurements are at 6- and 12-month intervals (379). With measurements intervals of 12 months or more, this calculation leads to an underestimation of age at PHV.

In growth studies, little attention has been paid to the *end of pubertal growth*. Some studies/growth models have used cut-off values based on previous growth to determine the end of the growth spurt. For example, the end of puberty may be considered to have been reached when growth slows to a rate equivalent to the lowest height velocity *before* the onset of the growth spurt, or when it reaches a level consistent with the mean height velocity during the years preceding the pubertal growth spurt (380, 381). When the declining height velocity after PHV reaches this value, then the end of the pubertal growth spurt has been reached according to these definitions. In the Taranger and Hägg study, they defined four different estimates for the end of pubertal growth; as explained in Figure I.28 (186). *Near adult height* is used as a final measure in many clinical studies, particularly those exploring the impact of GH-treatment. Near adult height is sometimes considered to be attained when height velocity becomes less than 5 or 10 mm/year, but it is often not clearly defined. Age when adult height is attained may also be used to define the end of the pubertal growth spurt.

Even less attention has been paid in studies of human growth to the *duration of pubertal growth* than has been paid to measures of PHV and the onset of pubertal growth. This is a natural consequence of the limited number of definitions available for the end of pubertal growth. In some studies, definitions of the duration of pubertal growth have only included the first part of the growth spurt; the time from onset of puberty to PHV (246).

In the absence of a definition for the end of pubertal growth, the *gain in height owing to pubertal growth* has generally been defined as growth from the onset of puberty until the attainment of adult height or near adult height. A more detailed analysis of height gain during puberty was lacking prior to the development of the QEPS model.

1.9 GROWTH MONITORING & GROWTH PREDICTION

Growth charts

A growth chart is the graphical presentation of a growth reference or standard (Figure I.31). Growth charts are important for the practical monitoring of height and weight in growing individuals.

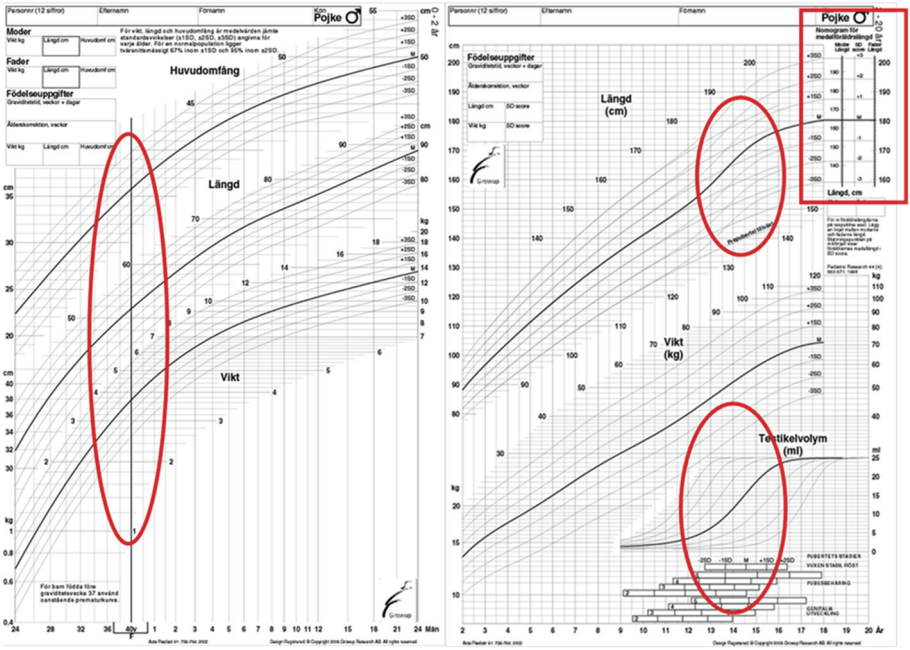


Figure I.31. Swedish growth chart for boys, aged 0–20 years. Ellipses highlight different decision making tools for the clinician. 1. Correcting for gestational age, From Niklasson A and Albertsson-Wikland K (92) for exploring variations in early growth due to gestational age. 2. For pre pubertal growth i.e. childhood component of the ICP model, From Karlberg J et al and Karlberg J (359, 361). 3. The pubertal growth spurt developed from a subgroup with narrow PHV range close to mean PHV, to obtain a more representative chart during the puberty period (as seen in Figures I.14 and I.24), From Albertsson-Wikland et al (372). 4 nomogram for sex dependent calculation of mean parental height/target height (top right). 5. At the bottom, there is a special growth chart for testicular volume and normal age intervals for pubertal stages, From Karlberg P and Taranger, J (157) aligned for a PHV 0,5 years earlier in the 1974 cohort. Figure courtesy of Professor Kerstin Albertsson-Wikland.

The first growth chart was invented in the US in the late 19th century (before that, normative growth data were presented in tables) (382). The first growth charts used presented a simple mean curve; from the 1920s, growth charts

were constructed that included mean height against age, as well as ±1 and ±2 SD curves (383). Today, growth charts generally include SDS or percentiles. Typically, the limits of normality are defined based on lines representing –2 to +2 SDS (2.25–97.5% of the reference) or the 3rd to the 97th centile. Some growth charts are, however, formatted differently; in Finland, growth is plotted in terms of SDS, so a child growing in line with the average follows the zero-line as seen in Figure I.32. (384, 385). In UK, growth charts provide percentile lines for the adolescent years (based on early, average, late puberty) to facilitate growth assessment during puberty. For taking both different pubertal timing into account and for limiting the Merrell bias, in the Swedish growth charts, the pubertal spurt is based on a narrow mean sub group of individuals, constructing a chart with steeper spurt, more assembling the pattern of individual growth during puberty (372).

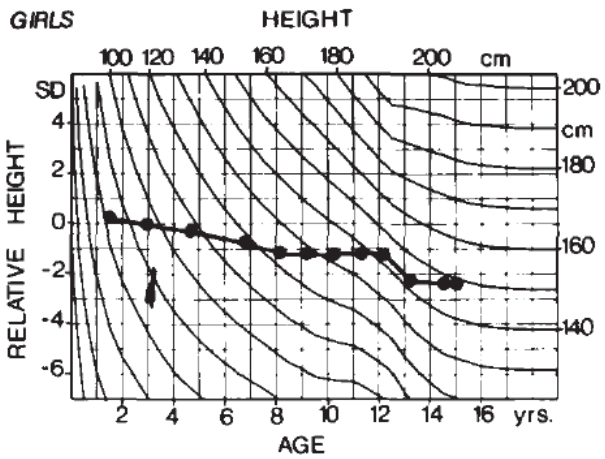


Figure I.32. Finnish height chart. Height-for-age reference for girls aged 1 to 20 years expressed as SDS values. The growth curve is plotted using height isometers (50–200 cm). From Sorva R, et al (385).

Some height references enable the user to plot the height of the individual in relation to mid-parental height (98). In 2000, Albertsson-Wikland et al. constructed a nomogram for calculating mid-parental height at the end of the chart, and by that obtain the target height in SD-scores, for the child (101, 372).

Growth monitoring – how to use growth charts

In many countries, the growth of infants and young children is measured on a regular basis, at WBCs or child healthcare centers (CHCs) as part of general preventive health care. Growth is also measured and monitored in school students around the world. This approach has been endorsed by the WHO, which has also developed international growth standards and conducted growth monitoring throughout the world (386).

There is a long tradition of growth monitoring; the first known description of longitudinal growth monitoring is the well-cited account of the growth of Count Montbeillard's son (3). Measurement of height and weight was introduced in schools in Europe and the US in the late 19th century. By this time, physicians and scientists on both sides of the Atlantic had started to view growth in children as a marker of health, disease and environmental/social factors (3, 234). In 1876, Charles Roberts proposed that overly short and thin children should not work in factories (3). In the early-to-mid 20th century, WBCs and CHCs were set up as part of the expansion of the welfare state, and in response to the growing number of babies being born in hospital by this time. Such centers began to be involved in the routine monitoring of growth in infancy and childhood.

Assessment of growth is based on comparison of the child's height or weight with that expected based on a growth standard or reference, and visualised in growth charts. The height and weight attained are each plotted on a reference chart that shows average growth and the normal spread of measurements in the reference population. In this way, it is possible to see how the child is growing relative to mean values, and to assess his/her position relative to the mean in centiles or SDSs. This provides answers to the question of whether the child is tall, average or short compared to his/her peers of the same chronological age. Repeated height measures are needed in order to evaluate growth; these allow us to answer questions such as is the child growing at a normal tempo (appropriate height velocity for age), and is the child maintaining the same position on the chart relative to the SDS-lines/centiles. In healthcare practice, the latter is often expressed in terms of whether or not the child is following his/her growth "channel" (see Figure I.31). When evaluating height and height velocity, weight is also of importance (see chapter 1.7); actual and previous measurements of weight should be

considered in the assessment of a child's height. Predicting systematically the impact of weight/BMI on further height gain has not yet been possible.

Evaluating the dynamics of growth, i.e. changes in height velocity, is much more challenging than evaluating stature. Several ways to assess alterations in the dynamics of growth have been proposed. These include assessing the existence of channel crossing and evaluating growth velocity at different ages. However, the high degree of variation in growth within and between children makes it difficult to identify a standard method of assessment. During the first year of life, for example, the growth of a healthy child may change by as much as 1 SDS, but later in childhood a change of this magnitude may be a sign of disease or psychosocial problems. Growth that crosses channels is often related to parental height, where the infant starting at a length above or below the mean of a growth chart, adjust its position to mid-parental height. This is typically seen in babies born later than 41 weeks or earlier than 39 weeks of GA. Since both height and weight in newborn babies are strongly correlated with GA, references correlating for prematurity (and late gestation) are essential when evaluating growth in infants born outside the average gestation. A reference correlating for GA was introduced in Sweden 2008, with growth charts from GA 24 weeks until 2 years of age, based on data from more than 800.000 selected healthy newborns (92, 387).

It is important to bear in mind the potential for measurement error when evaluating growth and height velocity. Errors may arise because of the use of different measurement techniques or because of differences between measurements made by individual measurers. They may also arise because of inaccurate plotting of measurements on growth charts, although the risk of this is lower with the standardised use of computerised growth charts than it was when all charts were paper-based. Inconsistencies between measurements owing to diurnal variations in height may also arise if height measurements are not made consistently at the same time of day (see subchapter *Diurnal variation in height* in chapter 1.2). Over a short time period, even a difference of 5 mm can have a major impact on calculations of height velocity.

To improve the quality of growth monitoring, centralised growth monitoring has been developed. CrescNet, a computer-based system for screening

electronic growth charts, was introduced by Keller in 1998 in Leipzig, Germany, with the aim of early detection of growth disorders. The system is integrated within many medical practices and pediatric endocrinology centers across Germany, and the growth data collected are sent to a database for central analysis (388, 389). CrescNet has been shown to be beneficial in identifying children with GH deficiency (390). Finland has developed an automated system to detect abnormal growth during childhood. The Finnish algorithm-based automatic growth monitoring system for assessing height SDS and comparing it to mid-parental height, as well as looking at delta height SDS was found to be superior to conventional clinical monitoring (391). The system detected pathological growth disorders earlier and more effectively than standard monitoring. Its application to data from the 1974 Swedish reference population, suggested that it would identify 3.3% of Swedish children with aberrant growth during childhood (392). During the adolescent years, the wide variation in pubertal timing also challenges growth monitoring and growth evaluation. If difference in tempo (pubertal timing) is not considered may individuals outside average puberty be misjudged, and some growth charts have been developed to solve this problem, considering different pubertal timing (372).

How to predict individual future growth?

From a clinical perspective, when dealing with growth failure and diseases that may affect growth, is it essential to be able to predict future growth. A very simple prediction of adult height can be made based on height at 2 years of age, assuming that the child has “found its position” on the growth chart by that age. The mid-parental height calculation gives the first prediction of how a child is expected to grow; however, although this defines the normal limits of adult height that will be attained, it does not provide insights into the path that growth will follow (101).

Assessment of BA may also provide information on maturity, where the assessment of future growth improves, especially later in childhood/during adolescence (338, 393). Determination of BA is commonly used clinically when evaluating and predicting growth in short stature, extreme tall stature, very early and very late puberty. The last decade has computer based automatic BA analysis of radiographic images been developed to improve accuracy and reproducibility (394, 395). Validated mathematical models

predicting future GH dependent growth have been developed for children receiving GH therapy to improve short stature (191, 366, 368, 396). These models use auxological measures, information about parental heights and the results of endocrine evaluations (GH, IGF-1) and sometimes BA to predict future growth. There are currently, however, no validated prediction models for treatment response of growth in other groups of individuals/for other diseases. The height/growth pattern of the child can be related to the height/growth patterns of the parents at the same age in selected clinical situations (Figure I.33). In cases where longitudinal measurements of height in parents are available, including these data may represent an improvement in growth monitoring; however, the value of this approach has not yet been scientific evaluated.

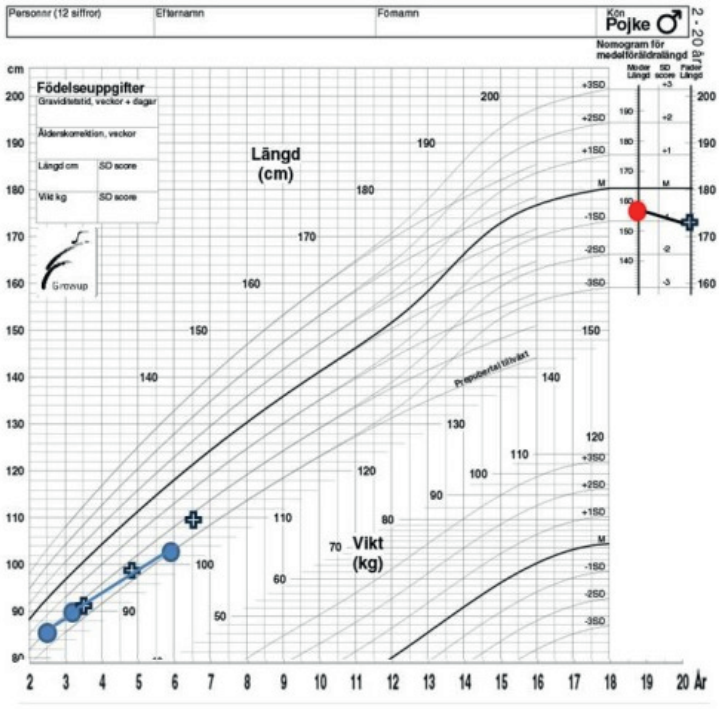


Figure I.33. Height of a boy plotted on a Swedish growth chart (blue circles) growing on a low height velocity, below -2SDS and deviating from 2.5 to – 6 years of age. The boy's growth growth curve is complemented by three height data from the father (cross). The fathers height at 5 and 7 years of age was slightly higher compared to that of his son (–2.5 to –2.3 SDS at these time points). The fathers adult height was much closer to the mean at –1.1 SDS; probably due to experiencing a somewhat later and/or more pronounced growth spurt than average. Figure courtesy of Associate Professor A. Stefan Aronson.

2 AIM

The overall aim of this thesis is to increase knowledge regarding human growth. Of particular interest is gaining a better understanding of growth during puberty, as well as exploring the influences of BMI in childhood on subsequent growth. An additional focus is exploring changes in height and growth patterns over time, both within and between populations (secular changes).

Specific aims

1.a Introduce and evaluate new estimates of pubertal growth (paper I).

1.b Explore pubertal growth in detail using new estimates from the QEPS model (paper I).

2.a Study associations between peak BMI in childhood and subsequent growth (paper II).

2.b Investigate how peak BMI in childhood is related to the timing and characteristics of the pubertal growth spurt (paper II).

3.a Investigate secular changes in height for Nordic countries and analyse during which growth phases (fetal/infancy/childhood/puberty) changes occur (paper III).

3.b Study secular changes during a longer period by comparing adult heights between the Swedish 1956-, 1974-, 1990 birth cohorts and their parents (paper III).

4.Evaluate changes in growth patterns from birth to adulthood in two Swedish population based cohorts born in 1974 and 1990, using the QEPS model (paper IV).

3 MATERIAL AND METHODS

The study material focused on within this thesis, and used within the four publications described, came from two large population-based studies that collected data in order to establish reference data on growth in Sweden; the GrowUp 1974 Gothenburg study and the GrowUp 1990 Gothenburg study (372, 397). Data used included longitudinal measurements of height and weight, together with information from the medical birth registry (MBR) and health questionnaires. In addition to conducting traditional analyses of height, weight and BMI, the QEPS growth model was used to construct individual growth curves and to analyse patterns of growth in terms of height over time in individuals. Paper III, which analyses height differences across the Nordic countries, also included data from growth studies in other Nordic countries published between 1976 and 2018.

3.1 THE GROWUP 1974 COHORT (PAPER I + III-IV)

The GrowUp 1974 Gothenburg study was conducted from April to November 1992; all high schools in Gothenburg were included. At this time, Gothenburg was the second largest city in Sweden with a population of approximately 500 000 and an annual birth rate of around 5000. Participants were high-school students in the 11th or 12th school years (mean age at inclusion, 18.1 years (372). Study teams visited schools; height and weight measurements were made using standard techniques and participating students were asked to fill in a questionnaire. The questionnaire asked about health/medical information (chronic illness), well-being and the height of the student's parents. School health care records and records from well-baby clinics (WBC), were consulted to obtain growth data prior to the study. A total of 5111 students were invited to participate; 3% declined to participate and 9% were absent from school. Participation rate was 86% based on completed questionnaires and 88% based on measurements. The study team at Gothenburg Pediatric Growth Research Center (GP-GRC) followed students who were not expected to have reached adult height at the time of measurement (mainly boys) for 1–3 more years.

Most participants (76%) were born in 1974; 17% were born in 1973, 3.6% in 1975 and 3.0% before 1974. Nearly all participants (97%) were born in Sweden and traced in MBR. The current Swedish growth reference was constructed based on data from this population; it included all healthy participants, born at term (GA, 37–42 weeks), for whom both growth data at birth and measurements made by the study team were available (3650 individuals). This growth reference has been used since 2000, with an updated version including a growth reference for newborns (GA, 24–42 weeks), published in 2008 (92, 372).

3.2 THE GROWUP 1990 COHORT (PAPER II-IV)

The GrowUp 1990 Gothenburg study was conducted from October 2008 to June 2009. Participants were high school students in the 12th school year (mean age at inclusion, 18.6 years) (397, 398). A majority of the high schools in Gothenburg, and the surrounding suburban municipalities of Härryda, Kungsbacka, Kungälv, Mölndal and Partille, participated. The population in the area in 2009 was approximately 670 000. (Figure M1). Study teams visited schools on at least two occasions; height and weight measurements were made using standard techniques and participating students were asked to fill in a questionnaire. The questionnaire asked about health/medical information (chronic illness), lifestyle (diet, meal pattern, sleep duration, physical activity), body perception, well-being, origin (country of birth for subjects and parents) and height of parents. School health care records and records from WBC were consulted to obtain growth data prior to the study. In total, 9179 students were invited to participate; 5% declined to participate and 32% were absent from school/ did not attend. Participation rate was 63% based on completed questionnaires and 59% based on measurements. Students who were not expected to have reached adult height at the time or measurement (mainly boys) were followed by the study team at GP-GRC for 1–3 more years. Most participants (85%) were born in 1990; 3.7% were born in 1991, 9.9% in 1989 and 1.6% from 1986–1988. Nearly all participants (93%) were born in Sweden. Individuals born from 1986–1988 were excluded from the study. Growth data from a selected subgroup of healthy children born at term to non-smoking mothers were used to construct the up-coming Swedish height reference (399).

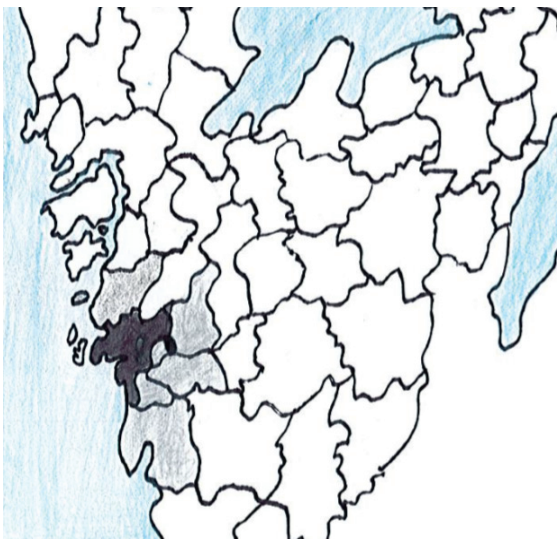


Figure M1. Gothenburg (dark grey) and surrounding participating municipalities (light grey) in the GrowUp 1990 study (with inhabitants representing 7% of the total Swedish population).
For location in Sweden, see Figure M.5.

3.3 DATA-SELECTION FROM THE GROWUP 1974/1990 COHORTS

In order to obtain comparable high-quality data from the 1974 and 1990 cohorts, individual height data and growth curves from all healthy participants of Nordic ethnicity who had been born at term (GA 37–42 weeks), and had data available both at birth and time of measurement by the in-school study team, were evaluated individually. Individuals selected for inclusion were required to have data available in pre-determined timeframes as outlined in Figure M2; at birth, infancy (two measurements), as a toddler, as a child (pre and post start of school), as a juvenile, as an adolescent and after 16 years of age (Group A criteria). Computerised selection was used to ensure that growth measurements were available for each of the different age periods. The Mathlab® software program was used with the QEPS-model formulae to calculate individual QEPS variables and to construct growth curves. Visual inspection of QEPS-model-fitted growth charts was conducted as shown in Figure M2.

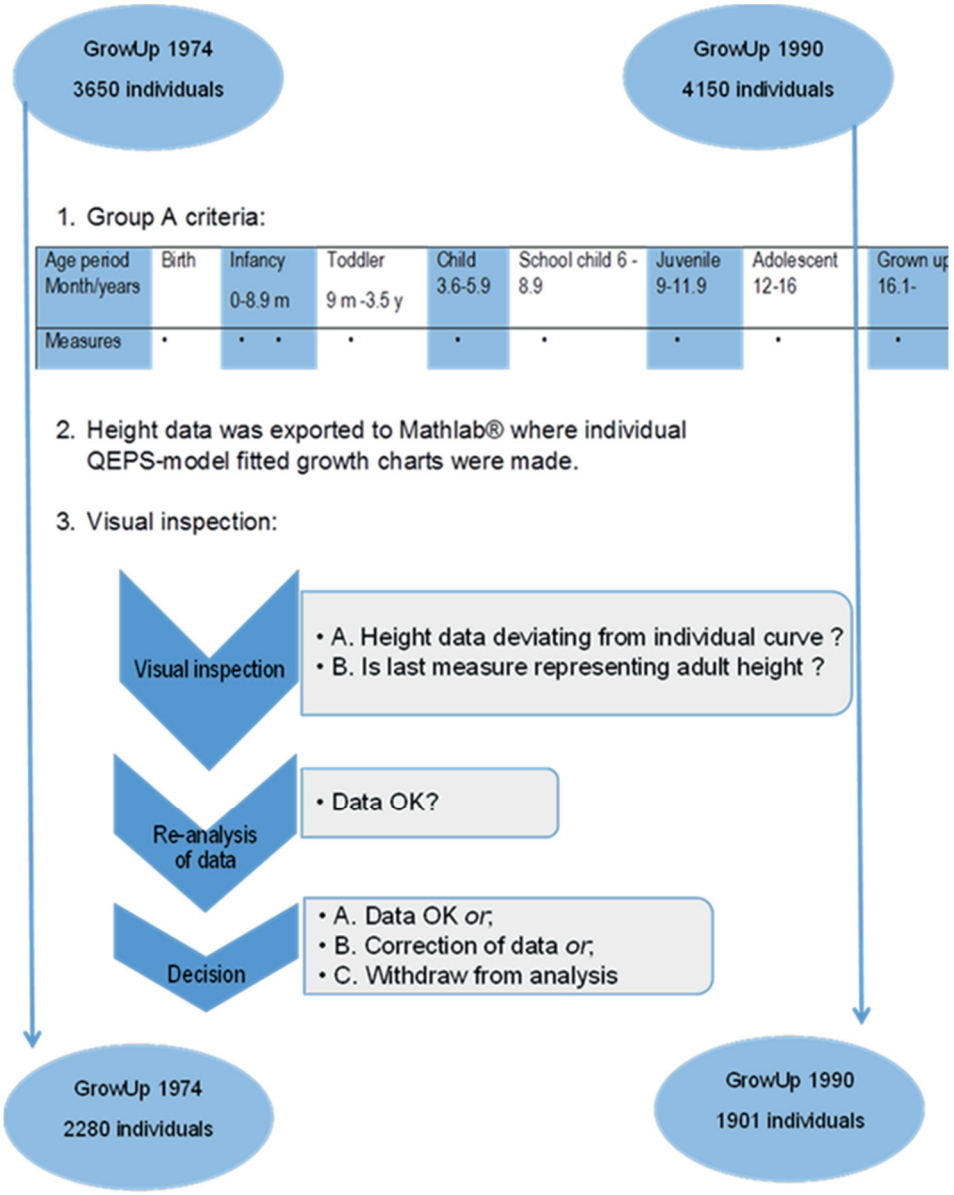


Figure M2. Selection of individuals from the GrowUp 1974 and 1990 populations with longitudinal height data available in all age periods.

A typical individual growth curve used for visual analysis is shown in Figure M3.

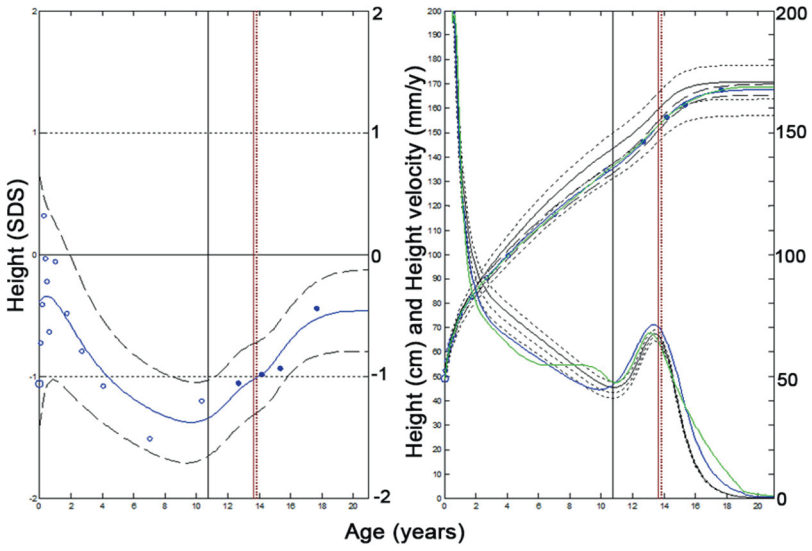


Figure M3. Example of an individual growth curve for a girl in the GrowUp 1974 cohort. Height in standard deviation scores, SDS (left panel), height velocity and height (right panel). Blue curves show the QEPS-calculated individual growth chart; small circles indicate actual height measurements. Black vertical lines show calculated onset of pubertal growth (*AgeT*$_{ONSET}$); red vertical lines show mid-puberty (*AgeP50*).

In total, 2280 individuals (1139 girls) were selected from the 1974 cohort; an average of 22 measurements were available per individual. In comparison, 1901 individuals (929 girls) were selected from the 1990 cohort; an average of 24 measurements were available per individual (Figure M4).

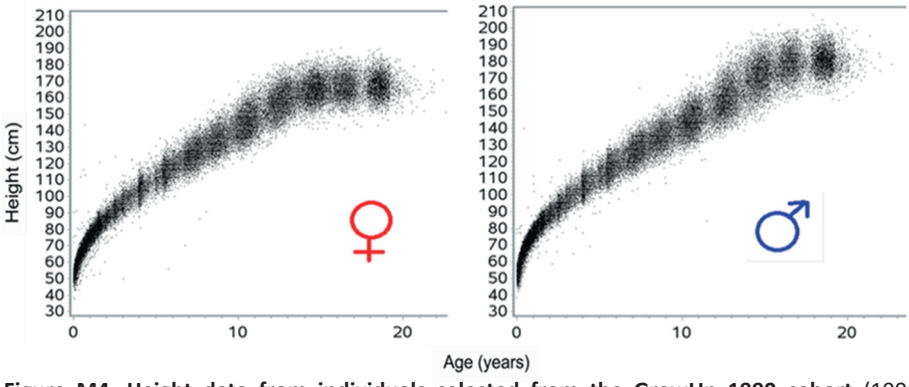


Figure M4. Height data from individuals selected from the GrowUp 1990 cohort (1901 individuals; females left, males right). Each height measurement is represented as a black dot; 45 349 measurements in total.

3.4 DATA OF HEIGHT IN NORDIC GROWTH STUDIES (PAPER III)

Study material for the paper on secular changes in height in Nordic countries was based on height data from growth studies on Nordic populations published during the last four decades. Data for Sweden came from the Grow Up 1974 and 1990 Gothenburg cohorts (described above in 3.1–3.2) (372, 397, 398), together with height data from growth studies on individuals born around 1956 and in 1981(188, 379, 400, 401). Height data for Denmark, Finland and Norway was taken from the publications in support of current and previous national growth references. Danish height data were taken from publications in 2014 and 1982 (231, 232). Finnish height data came from publications in 2011 and 1990 (384, 385, 402). Data for Norway came from publications in 2013, 1983 and 1988 (229, 403, 404). Iceland has not published growth references at different time points during the last decades; therefore, height data from Iceland was not analysed. Main centres for the growth studies are shown in Figure M5. Data on the height of participant's parents were analysed, where available, to study secular changes in adult height; this was possible for the Swedish growth studies from 1956, 1974 and 1990.

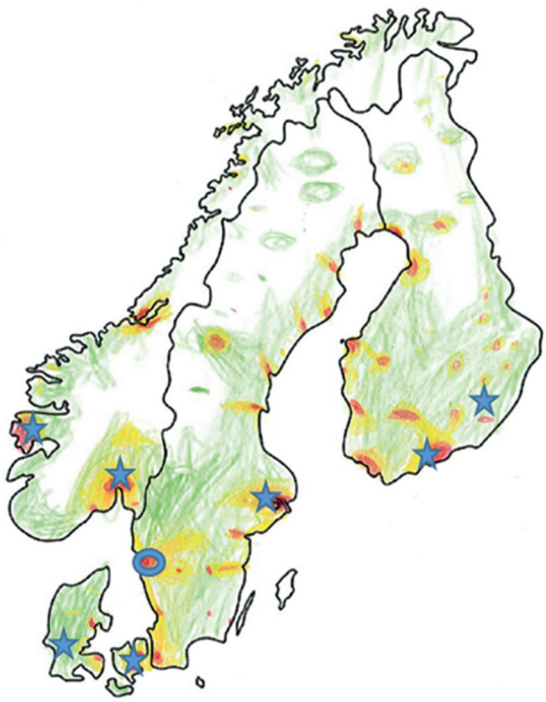


Figure M5. Demographic map of the Nordic countries (colours indicating populated areas from highest to lowest density; red–yellow–green–white). Gothenburg is indicated by a blue circle and areas where other Nordic growth studies were conducted

are marked with blue stars.

The Swedish 1956 height reference

Published in 1976, the Solna growth study followed children born in and around 1956; data from this population formed the growth reference used in Sweden prior to the current reference (188). It was a prospective, longitudinal study, in which pregnant women were asked to participate alongside their expected infant, and was part of a European collaboration, with similar studies being conducted in Brussels, London, Paris and Zurich (280, 371). The infants included were born between 1954 and 1958 (a majority born in 1956). The study included 212 individuals; three children were excluded (two due to obesity, one due to a cranio-fascial malformation) and 39 were lost to follow up before 18 years of age, mainly due to migration. Somatic, psychological and social investigations for each participant were undertaken repeatedly by a special study team, and bone maturation (X-ray) and pubertal stage were also assessed (157). Many different anthropometrical measures were recorded (for example; sitting height, biacromial width, head circumference, biceps skinfold). Height values analysed in this thesis (Paper III) are based on the original publication and the growth reference charts that were distributed for use as growth references in Sweden from 1977 to 2002. Follow up height measurements at 21 and 25 years of age were available for 155 individuals from this study (379). The height of participant's parents was measured in the original growth study; however, raw data were not available, so the parental height data analyses were based on the mean values reported (374).

The Swedish 1981 height reference

Published in 2006, the Swedish 1981 growth study provided descriptive, representative growth data from all over Sweden based on a study cohort comprising all individuals born on the 15th of any month in 1981, and living in Sweden in December 1989 (400). Data were captured from birth to 19 years of age, with height and weight (head circumference at 0–2 years) being obtained from WBC/school health records. Data on height and weight at birth were available from 98.4% (3107) of the 3158 children identified based on birth date. In order to construct a representative growth reference, infants with a birthweight below 2500 g, children with chronic diseases affecting growth (n =24), and those born outside Sweden were excluded. The remaining 2539 individuals were used as the reference population. Information on males was supplemented with data (height and weight) from the Conscript Registry. In total, a mean of 22 height measurements were

available per individual. Data from this population has served as one of the growth references in Sweden since 2007.

The Danish growth references

Published in 1982, the 1953–1972 Danish growth reference was based on data (height and weight) obtained from WBC/schools from 13 719 individuals born between 1953 and 1972 (232). The included individuals came from different parts of Denmark, the capital Copenhagen, the city of Randers and rural areas. Children with chronic diseases and a BW below 2500g were excluded from the study group constituting the growth reference. The data were semi-longitudinal.

Published in 2014 by Tinnggard et al., the current Danish growth reference was constructed based on data from two prospective studies (the Copenhagen puberty study and the mother–child cohort); information on males was supplemented with adult height data from army conscripts. In total, the study captured 12671 measurements from around 5000 individuals (231). Females included in the population used were born from 1987–2002 and males from 1977–2002. Length/height and weight measurements were a mixture of semi-longitudinal and cross-sectional data, with measurements made by a study team (except for data from military conscripts). For females, adult height data was either based on actual measurements or estimates from measurements during adolescence. Individuals born at a GA <37 or >42, with non-Caucasian ethnicity or chronic diseases were not included in the data set used to construct the growth charts.

The Finnish growth references

Published in 1990, the Finnish growth reference of Sorva et al. was based on semi-longitudinal data (length/height and weight), from around 2100 individuals born from 1959–1961 and 1969–1971, obtained from WBC/schools in Helsinki and eastern Finland (384, 385). For males, information on adult height was supplemented with data from conscripts aged 18–20 years. Chronic diseases, 'major abnormalities' and a birth weight below 2500 g were exclusion criteria.

The current Finnish growth reference of Saari et al. (2011) is based on semi-longitudinal data (length or height and weight; 181 785 measurements) collected at WBC and schools from 26 636 individuals born from 1983–2009 in the city of Espoo (402). For males aged 18–20 years, information on height was supplemented with data from conscripts. Exclusion criteria were

birth before 37 weeks GA, unknown birth weight or birth weight below 2500 g, height outside ± 4 SD of the mean, being underweight or obese and showing abnormal growth (according to specified definitions). Data included immigrants, estimated to be 5.6% of the population.

The Norwegian growth references

The old Norwegian growth references by Waaler (1984) was based on a prospective, cross-sectional/semi-longitudinal study in which measurements were made by a study team at WBC/schools in Bergen from 1971–1974 (229). In total, 3068 children (8414 measurements; range, 1–4 measurements/child) were included. Children with "diseases or malformations affecting their general condition severely" were excluded. Data were available until 16.9 years of age. Data on growth from 0 to 4 years of age were supplemented by information from the 'SYSBARN' study by Knudtzon et al., which included growth data from 23 669 healthy infants/children born in Oslo (403).

The study to develop the current Norwegian growth reference by Juliusson et al. (2013) was similar in design to that used to develop the 1984 reference; data were cross-sectional/semi-longitudinal, with measurements made by a specialised study team in 7291 children/adolescents from Bergen (404). Invitations were sent to WBC, kindergartens and schools; participation rate was 98% in WBC, falling with age to 45% in secondary schools. Data from children with GA < 37 or >42 week, chronic diseases and those with one or both parents born outside Norway, were not used to construct the growth charts.

3.5 MEASUREMENTS AND BMI CLASSIFICATION

Height, weight and BMI

School-based measurements of participating individuals around 18 years of age in the GrowUp 1974 and 1990 studies were performed by specially trained teams. Height was measured to the nearest 0.1 cm using a calibrated Harpenden stadiometer, and the mean of three independent measures was used. Team members were instructed to make repeated measurements of each participant until three consecutive measures were within 0.5 cm difference. Weight was measured to the nearest 0.1 kilograms (kg). Growth data prior to the study team measurements were obtained from WBC/school health records as described in section 3.1–3.2. Data on height, weight and BMI were converted to SDS using the reference created from the GrowUp 1974 cohort so that growth measures were independent of age and gender (294, 372).

Adult height was defined as having been attained when there was a height increase of less than 0.5 cm during the previous 12 months. Individuals who were still growing (mainly boys) were followed with additional measurements by the study team at GP-GRC until adult height was attained.

Data on the height of participant's parents were collected via questionnaire, and recorded in cm. SDSs were calculated relative to adult height in the 1974 growth reference.

Childhood BMI classification

Since BMI during childhood is generally much lower than in adulthood, and has an age-specific pattern, with the lowest mean values being around 5–6 years of age, it is beneficial to use BMI_{SDS} instead of crude BMI values in paediatric clinics and research (see chapter 1.7). Hence, in paper II crude BMI values were transformed to BMI_{SDS} to yield age- and gender-specific BMI-scores (293, 294). For the calculations, the highest BMI_{SDS} obtained between 3.5 and 8.0 years for each boy and between 3.5 and 7.0 years for each girl, was used (Figure M6). The use of a different age range for boys and girls was due to the difference between the sexes in the timing of puberty.

The International Obesity Task Force (IOTF) BMI classification was used to define subjects as obese (Ob), overweight (Ow), normal weight (Nw), and underweight (Uw) (293). In order to analyse increases in height relative to BMI in childhood, data were shown both as a continuum, showing the highest BMISDS for each child, and with the study population divided into Overweight–Obese and Normal weight–Underweight subgroups.

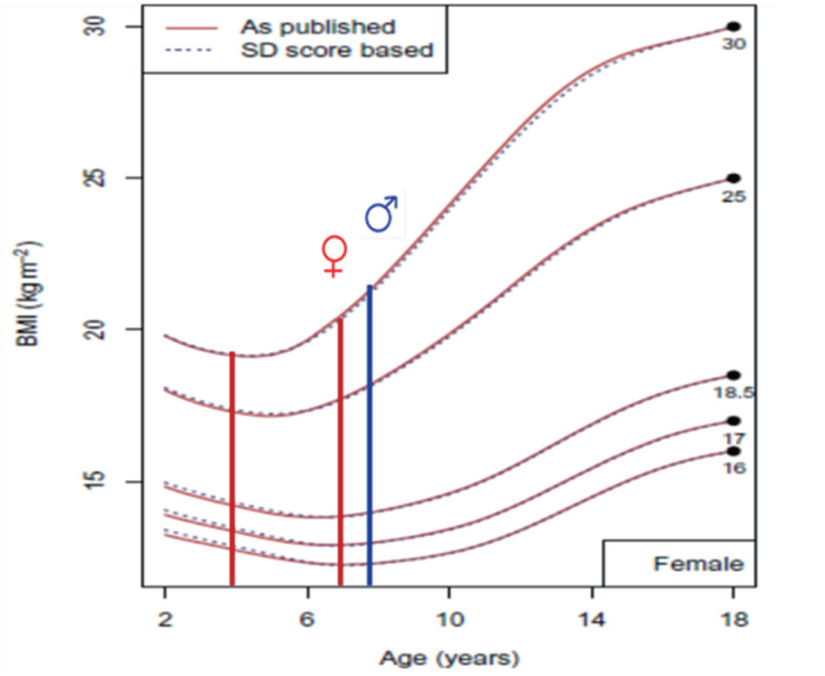


Figure M6. BMI levels representing children who were obese (≥ 30), overweight (≥ 25) and underweight (≤ 18.5) during childhood and adolescence. Vertical bars showing the years for highest used BMI_{SDS} value in paper II. Modified from Cole and Lobstein (292, 293).

3.6 THE QEPS GROWTH MODEL

The QEPS-model describing individual growth is constructed using a combination of four basic growth functions describing total height (T) in cm as a function of age; T(age) = Q(age) + E(age) + P(age) − S(age). The Q-function and the negative exponential E-function both start during fetal life, 8 months before birth; the E-function levels off after birth, whereas the Q-function continues until the end of growth. A specific pubertal P-function starts at the onset of puberty, and growth during puberty is determined by the continuing Q-function and the specific P-function (Figure M7). A stop S-function ends growth. For the E-, Q- and P-functions, an individual height-scale parameter is defined, and for the E- and P-functions, a time-scale parameter; together with individual timing of puberty (*AgeP50*) giving six modifying parameters, which made it possible to model individual growth curves from birth to adult height.

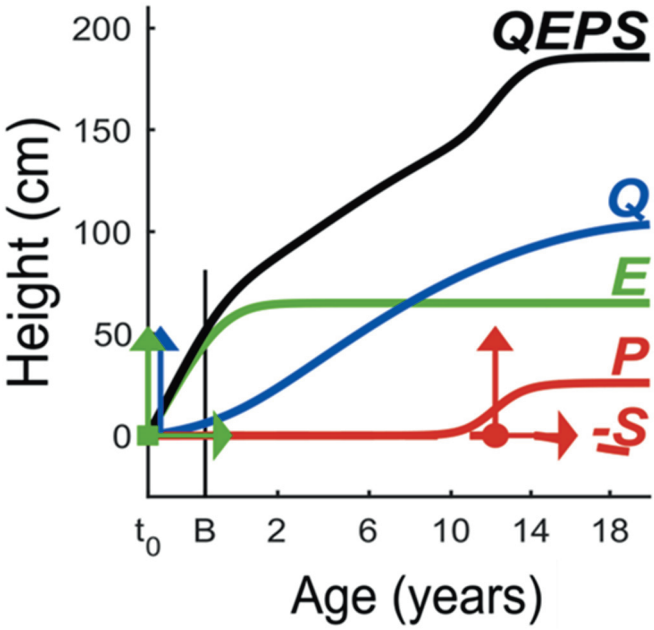


Figure M.7.QEPS model. The total height (QEPS) is the sum of four growth functions: Quadratic (Q), Exponential (E), Pubertal (P), and Stop (S). B = birth, t0 = about 6 weeks after conception. The vertical arrows indicate the individual height-scale parameters of the E, Q and P-functions, the horizontal arrows indicate the individual time-scale parameters of the E, and P-functions. The individual location of mid puberty *AgeP50* is marked as a dot. Birth is marked with a vertical line.

Mean height data of the GrowUp 1974 reference (n=3650) was used to construct the growth functions and the theoretical QEPS tool. For the pubertal period, values were based on data from a subgroup of children within the reference population with a narrow age range (0.5 years) at time of PHV. These data were supplemented with mean height data for the gestational period (weeks 24–40) from the healthy Swedish population born between 1990 and 1995 (92).

The four different height scales (one for each growth function) make it possible to model individual differences in size (height), and the time-scale functions of the E- and P-functions, enable individual differences in tempo (catch- up/catch down growth in infancy and pubertal growth) to be visualised, as seen in Figure M8. The different growth functions can be described both in cm or years and in SDS related to the mean (in the supplemental QEPS model paper similar to SP-scores). By adding height measurements of an individual, the QEPS model calculates individual growth curves and QEPS functions.

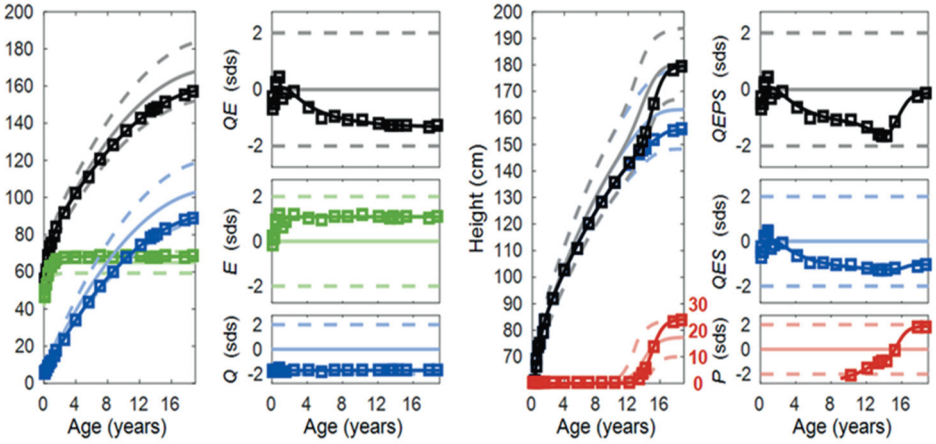


Figure M8. Example of a boy with high E-function, low Q-function, late and high P-function. Grey solid lines showing mean values, dashed lines ±2 SDS. The growth curve is shown both as height in cm and as SDS. Left panel show Q (blue), E (green), and their sum QE (black). The long *Etimescale* can be seen as catch-up of the E-function in SDS during the first years of life in ESDS and catch-up of the QE-function in QESDS. The low Q-function in QSDS, resulting in a decrease of the total QE-function in SDS after the initial catch-up. Right panel show P (red), QES (blue), and their sum QEPS (black). The P-function is starting later than average and is higher than the mean resulting in an increase of the total QEPS-function (height) during puberty.

To construct longitudinal growth curves, the Matlab® software program was used (version 7.13.0 R2012b, The Mathworks). The Matlab Curve Fitting Toolbox is used for regular curve fitting, with estimations of 95% confidence intervals (CI) for the fitted parameters, allowing the possibility of defining more objective criteria for evaluating data reliability. A more detailed explanation of the QEPS model can be found in the Appendix of this thesis (1). An in depth description of the QEPS estimations for pubertal growth, and the importance of CIs and SDS for describing and analysing pubertal growth, is presented in the chapter 4.1.

3.7 STATISTICAL ANALYSES

In paper I, measured and calculated pubertal growth variables were presented as mean, median, SDS, maximum and minimum, with lower and upper 95% CIs, with skewness and kurtosis computations given in the supplemental information. Student's two-tailed t-test was used to compare birth characteristics, growth estimates from the QEPS-model and adult heights for weight status dichotomised into the Overweight–Obese and Normal weight–Underweight groups in paper II. For variables with skewed distribution, nonparametric tests were used (Mann-Witney U test) . The same tests were also used to compare birth characteristics, growth estimates from the QEPS-model, heights during childhood/adult height for the 1974/1990 growth cohorts in paper III, and for the comparisons of adult height/parental heights for the 1974/1990 cohorts in paper IV. In all papers, statistical analyses were performed using SAS software® (SAS Institute Inc., Cary, NC, USA, version 9.3). A p-value <0.05 was considered statistically significant.
For countries other than Sweden in paper III, statistics could not be calculated based on data available in the publications. To compare changes over time, the difference in attained height between the last and first cohort was calculated and divided by the time between by decade. When comparing changes in adult height over time (separated by sex), the time period between the two studies was calculated based on the mean year of birth for the individuals used for adult height within each study (i.e. Solna 1956, mean year of birth 1956 (1954–58), GrowUp Gothenburg 1990, mean year of birth 1990 (1989–91), 1990–1956 = 34 years). The difference in mean adult height between the past and present study group where then calculated. By dividing the difference in height by the time in years between the studies, a difference per decade was obtained (i.e. Solna 1956, mean adult height 180.1 cm versus GrowUp Gothenburg 1990, adult height 181.7 cm; difference 16 mm, per decade; 16/34 =4.7 mm/decade).

4 RESULTS AND COMMENTS

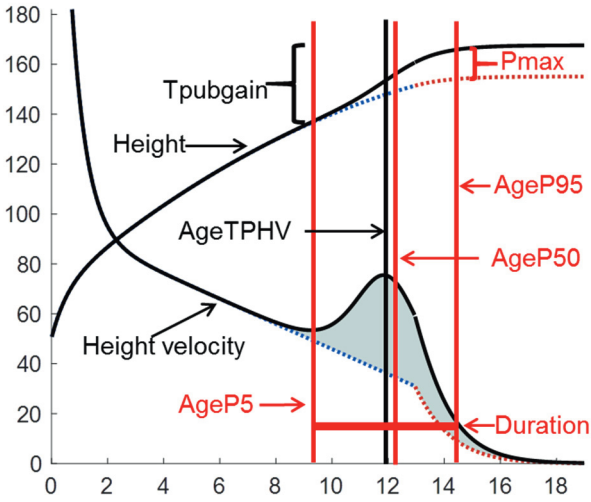


Figure R1A. Some basic pubertal growth estimates from the QEPS model, exemplified in the height- and height-velocity graph of an individual male. Height (cm) and height velocity (mm) on y-axis, age (years) on x-axis. *Tpubgain* shows the total growth during the pubertal years, *Pmax* shows the specific pubertal height gain, and *AgeTPHV* denotes the age at which growth velocity was highest during the whole growth period. *AgeP5* indicates the point where 5% of specific pubertal growth was attained, *AgeP50* indicates where 50% of the specific pubertal height gain was attained, and *AgeP95* indicates where 95% of specific pubertal growth was completed. The duration of pubertal growth can be calculated as the time between *AgeP5* and *AgeP95*.

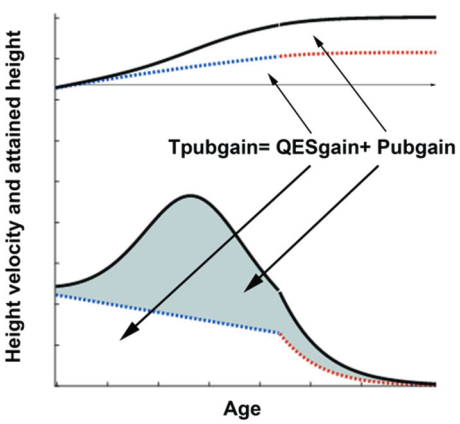


Figure R1B. Different measures of pubertal height gains from the QEPS model. *Tpubgain* (see R1A.) can also be visualised as the area under the curve in a height velocity graph, as the sum of *QESgain* and *Ppubgain*. The specific pubertal part *Ppubgain* in grey, *QESgain* below the dotted blue line.

Insights into pubertal growth from the QEPS model (Paper I)

The manuscript describing the application of the QEPS model to growth data has a dual purpose; it provides both a methodological description of the QEPS model and how it provides novel measurements of pubertal growth, and an in depth analysis of pubertal height patterns. The analysis uses individual longitudinal height data from a subset of the GrowUp 1974 Gothenburg cohort (2280 individuals with good longitudinal height data). This study will be referred to as the *QEPS-puberty study* in this thesis.

Rationale

The pattern of growth that occurs during puberty is unique to humans. Changes in height follow an S-shape pattern. This pattern reflects the change from the slowly decreasing height velocity typically seen in childhood, through the increase in height velocity that accompanies the pubertal growth spurt (for details see Figures I.1, I.15), to the slow decline in height velocity that occurs towards the end of growth. Around 2 years after the onset of puberty, height velocity reaches a peak, termed peak height velocity (PHV), following which it declines progressively until adult height is attained. Because height gain during adolescence is known to be related to the hormonal and physiological changes of puberty, the pubertal growth spurt can be used as a marker of puberty. There is wide variation between the sexes in the timing of pubertal growth, both between and within populations. Both the sigmoid shape and wide variation in pubertal timing have presented challenges when describing changes in height during this period in previous growth models.

Previous growth models have allowed limited modeling of individual differences in height gain during the pubertal years. The ICP-model, for example, can model individual differences in the timing of onset of puberty; however, it assumes that the specific pubertal height gain component is fixed (10.9 cm for girls; 15.4 cm for boys), with no option for individual variance

in the gain in height during the pubertal years (358). In fact, no previous growth models used mathematically derived parameters to evaluate growth across puberty. In addition, despite the use of SDSs as standard when evaluating measurements of height and weight, no growth models or mathematical models prior to QEPS had derived SDSs to describe differences in growth tempo and timing of pubertal growth. Existing growth models also lacked measures of the precision of individual calculated parameters, such as individual confidence intervals (CI). The QEPS growth model can automatically calculate specific pubertal growth (via the P-function in QEPS) and ongoing basic growth (via the Q-function in QEPS) during the adolescent years. QEPS is also able to describe individual variation in the timing and duration of pubertal growth, as well as the height gained, and can provide measures both in cm/years and in SDSs with individual CI. Some pubertal growth estimates from QEPS are shown in Figure R1. The aim of the *QEPS-puberty study* was to describe and analyse novel measurements of height gain during puberty, allowing for precise individual description of pubertal growth patterns, such that the information gained is useful for both research and clinical practice.

Results

Onset of pubertal growth

Three novel measures that can be used to estimate the onset of pubertal growth were calculated using the QEPS model, as shown in Figure R2. $AgeT_{ONSET}$ was calculated from the total growth curve as a measure of the point at which the declining height velocity associated with childhood growth (Q-function) is reversed by the onset of the pubertal growth spurt (P-function). *AgeP1* and *AgeP5* were calculated from the specific pubertal growth function (P) and represent 1 and 5 %, respectively, of the total specific height gain during puberty; these parameters can be used to estimate the onset of the pubertal growth spurt. For girls, the first onset measure was *AgeP1*, occurring at a mean age of 8.71 years, age at $AgeT_{ONSET}$ was 9.24, and *AgeP5* was 9.84 years. For boys, $AgeT_{ONSET}$ and *AgeP1* did not differ (mean age, 10.74/10.73 years), *AgeP5* occurred at a mean age of 11.78 years (Figure R2).

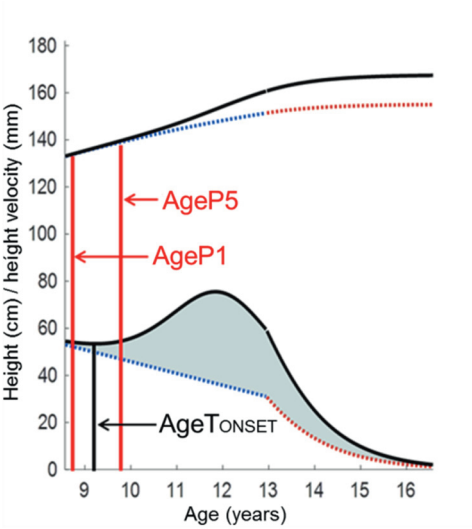


Figure R2. The three growth estimates for the onset of pubertal growth from the QEPS model exemplified in the chart for height and height velocity for an individual girl. *AgeT$_{ONSET}$* is calculated from the total growth curve, a measure when height velocity is at its nadir, from declining to increasing, indicated by a black arrow. *AgeP1* and *AgeP5* are when 1 and 5% of specific pubertal growth has been attained, respectively, indicated by red arrows.

Mid-period of pubertal growth

Three novel measures that describe the midpoint of puberty were presented in the *QEPS-puberty study* and are shown in figure R3. The QEPS model can calculate the age at PHV from both the total growth curve (*AgeTPHV*) and the specific P-function (*AgePPHV*). In addition, mid-puberty can be estimated based on the point at which 50% of P-function-related height gain has been reached (*AgeP50*). The study compared the new measures with the older visual-based estimates of PHV as used in the ICP-model. Mean values for all measures were close to each other; range, 11.83–12.09 years for girls and 13.66–13.83 for boys, as shown in the Table R1.

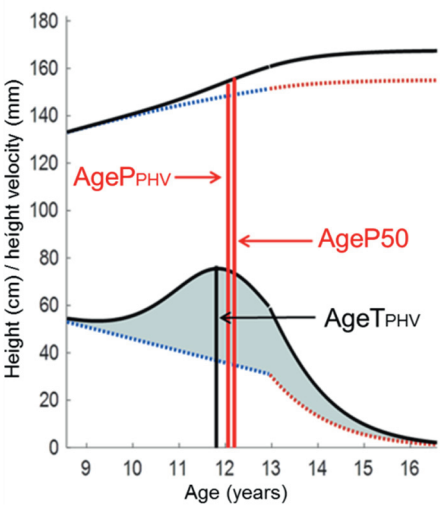


Figure R3. The three estimates of mid-pubertal growth from the QEPS model exemplified in the chart for height and height velocity for an individual girl. *AgeTPHV* is calculated from the total growth curve, a measure when height velocity is maximal, equal to the traditional, visual-based PHV measure, indicated by a black arrow. *AgeP50* represents when 50% of total P-function-related growth has been attained, and *AgePPHV* represents that age at which height velocity owing to the specific P-

function is calculated to be maximal, indicated by red arrows

Table R1. Mid pubertal growth estimates (age in years)

	Girls			Boys		
Variable	**Mean**	**Median**	**SD**	**Mean**	**Median**	**SD**
AgePHV[1]	11.92	11.88	0.97	13.83	13.81	1.00
AgeTPHV	11.83	11.80	0.96	13.66	13.65	0.96
AgePPHV	12.02	11.98	0.95	13.73	13.72	0.96
AgeP50	12.09	12.06	0.95	13.80	13.78	0.96

Values are age in years. [1] =Visual estimated PHV from the ICP-model

End of pubertal growth

In addition to providing measures of the onset of puberty, the P-function of the QEPS model provided measures of the end of pubertal growth (*AgeP95*, *AgeP99*). A third measure, $AgeT_{END}$, which represents the time where height velocity has decreased to 1cm/year, was derived from the total growth curve.

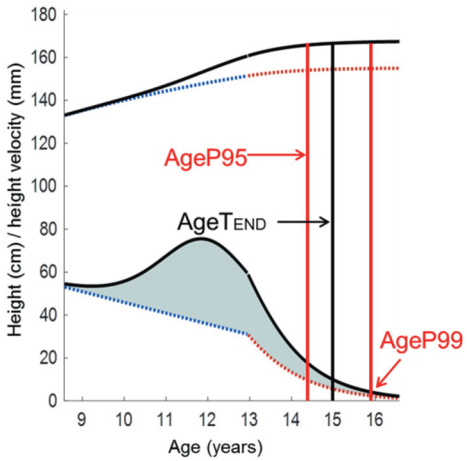


Figure R4. The three growth estimates for the end of pubertal growth from the QEPS model exemplified in the chart for height and height velocity of an individual girl. $AgeT_{END}$ is calculated from the total growth curve, a measure when height velocity is below 1cm/year, indicated by a black arrow. *AgeP95* and *AgeP99* are when 95 and 99% of the specific pubertal growth has been attained, respectively, indicated by red arrows.

Duration of pubertal growth

The QEPS model was used to calculate the duration of pubertal growth in years based on the different estimates for the onset and end of pubertal height gain. A clear sex difference was seen in both the timing and duration of pubertal growth, with the pubertal growth spurt for boys being later and

shorter than for girls. Based on *AgeP5* and *AgeP95*, the mean duration of the growth spurt was 4.80 years for girls and 4.32 years for boys (Figure R5).

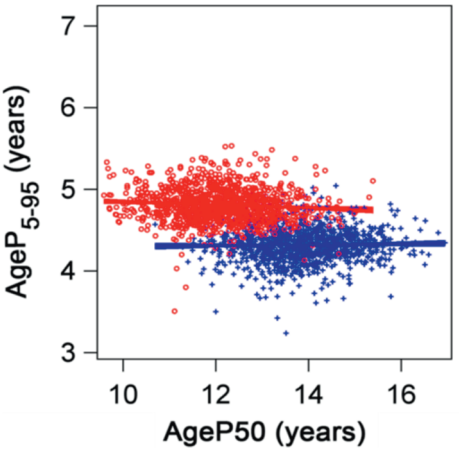


Figure R5. The relationship between the duration of pubertal growth and AgeP50. The time from AgeP5 to AgeP95 for girls (red circles) and boys (blue crosses) in the study population, represents the duration of pubertal height gain (From paper I, Holmgren et al. BMC Pediatrics (2017) 17:107).

Gain in height during the pubertal years

The total gain in height during the pubertal years was calculated as the increase in height from the total growth curve between *AgeP5* and *Age95* (called *Tpubgain*) or between *AgeP1* and *Age99*. Another way of defining growth during puberty is as the increase in height between $AgeT_{ONSET}$ and adult height. Pubertal height gain was also described in terms of what the specific P-function (*Pmax*) adds to the ongoing QES-function (Figure R1). The mean values of the different estimates for pubertal gain are shown in Table R2.

Table R2. Estimates of pubertal height gain (cm)

	Girls			Boys		
Variable	**Mean**	**Median**	**SD**	**Mean**	**Median**	**SD**
Pmax	12.78	12.73	3.65	17.34	17.48	3.63
Tpubgain (AgeP5-P95)	26.34	26.35	3.81	29.00	28.97	3.64
Gain *AgeP1-AgeP99*	33.64	33.57	4.56	35.62	35.55	4.26
Gain *AgeTONSET*-AH	31.51	31.54	5.34	36.09	36.10	4.89

Values are height in cm. AH =Adult height.

When the pubertal period was defined based on the time period between *AgeP5* and *AgeP95*, growth in girls was predominantly a result of the QES-function, while in boys growth was predominantly attributable to the P-function; however, there was large inter individual variation for both sexes (Figure R6).

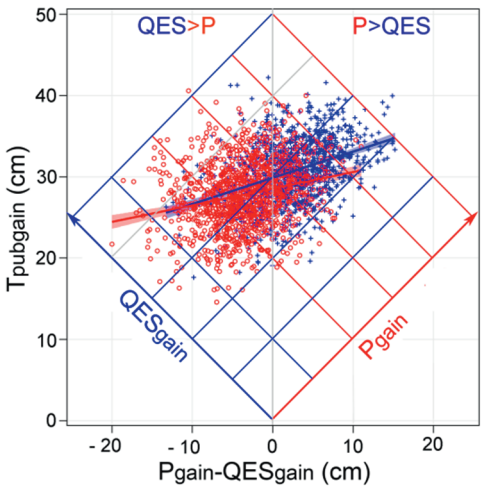


Figure R6. The Relationship between *Pgain* (= 90% of *Pmax*) and gain from the Q-function during the pubertal years (*QESpubgain*) showing the total height gain during puberty (Tpubgain). Relationship is expressed as a subtraction on the horizontal axis (cm) and total pubertal gain (cm) on the vertical axis. If *Pgain* = *QESpubgain*, then the difference is zero. Different combinations of *Pgain* and *QESpubgain* resulting in different total pubertal gain that can be evaluated using the transverse lines for each variable. The oblique blue line, with its transverse blue isolines, represents *QESpubgain*, and the oblique red line, with its transverse red isolines, represents *Pmax*. Red circles indicate girls, blue crosses indicate boys.

Height gain & adult height related to the timing of pubertal growth

The increase in total height during the pubertal years; *Tpubgain*, was higher for individuals of both sexes with earlier puberty compared to those with later puberty. The specific pubertal gain, *Pmax* was not influenced by the timing of puberty (Figure R7).

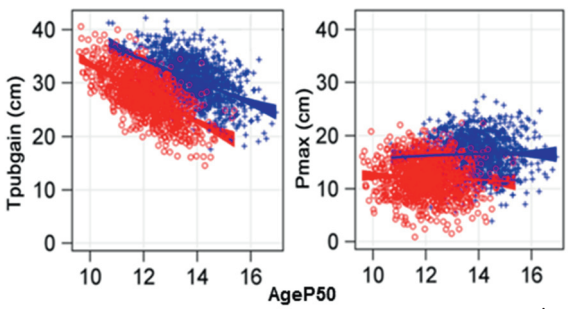


Figure R7. Total height gain in puberty (*Tpubgain*) from *AgeP5* to *AgeP100* (left panel), is related to *AgeP50*. For girls; *Tpubgain* = 59.823 – 2.647× *AgeP50*, adjusted r2 = 0.395. For boys; *Tpubgain* = 58.142 – 1.988x *AgeP50*, adjusted r2 = 0.253. The right panel shows the relationship between *Pmax* and *AgeP50. For girls; Pmax = 14.393 – 0.1850× AgeP50, adjusted r2 = 0.0019. For boys; Pmax = 15.243 + 0.0917 x AgeP50, adjusted r2 = −0.0002.* Red circles indicate girls, blue crosses indicate boys.

For both sexes, taller adult heights were found in individuals with later pubertal growth, however, there was broad individual variation and apparent differences in the distribution of pubertal timing between females and males, as seen in Figure R8.

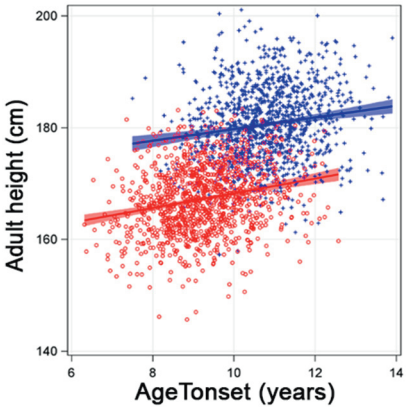


Figure R8. Onset of pubertal growth and adult height. Age at the minimum height velocity before the pubertal growth spurt ($AgeT_{ONSET}$) for girls (red circles) and boys (blue crosses) is related to adult height. For girls; adult height = 156.64 + 1.189 x $AgeT_{ONSET}$, adjusted r^2 = 0.0376. For boys; adult height = 171.87+ 0.818 x $AgeT_{ONSET}$, adjusted r^2 =0.0131.

A 1-year delay based on $AgeT_{ONSET}$, gave an adult height that was greater by 1.2 cm in girls and 0.8 cm in boys. The pattern was similar when comparing other estimates of onset of puberty and mid pubertal growth.

SDS for individual description of pubertal timing & growth estimates

In addition to the conventional description of height gain related to chronological age, pubertal growth can be visualised after adjustment for the time of onset of puberty. Using the QEPS model, the growth of an individual was related to the mean age at onset of puberty (zero) in a reference population (Figure R9). This gave the option to describe relative pubertal age. For each individual, all estimates were described in terms of SDSs, in addition to being described in cm and years.

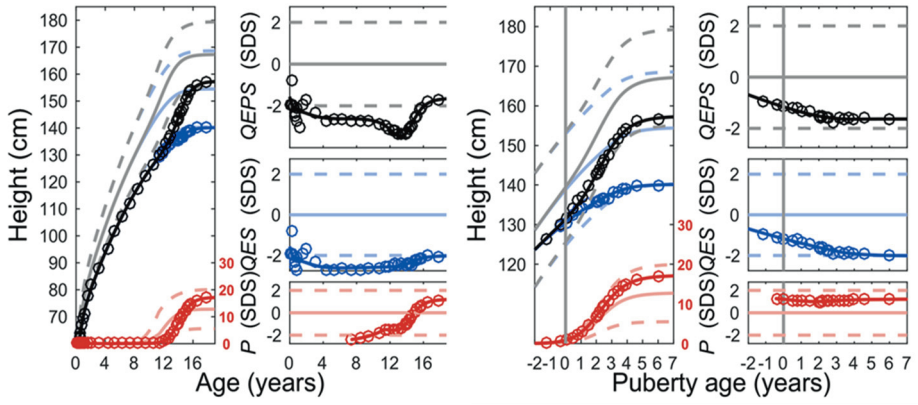


Figure R9. The total growth of a girl with the growth functions related to chronological years (left panel), as well as relative pubertal age (right panel). Relative pubertal age, 0 is defined from AgeP5. The upper solid black lines indicate the individual total height expressed in cm in to the left and heightSDS, to the right with the actual height measurements indicated as circles. The gray solid line indicate the mean, the dotted gray lines represent ± 2 SDS. The solid blue line shows the individual height QES-function expressed in cm and heightSDS, the solid light blue line the mean QES values, and the dotted light blue lines ± 2 SDS. The solid red line shows the individual specific P-function expressed in cm and heightSDS, the solid light red line showing the mean P-values, and the dotted light red lines represent ±2 SD. The girl has a low QES-function from -2 to -2.5 during childhood, with a late but high P-function, heightSDS +1.2, resulting in an adult height of -1.7.

Individual CIs showing precision of estimated values

The QEPS model can calculate individual CIs for every pubertal growth estimate as a marker of the precision of the value. The relationship between *AgeP50* and its corresponding CI showed that the CI increases in adolescents with higher *AgeP50* (i.e later pubertal growth); this was particularly evident in girls. Thus, there is greater uncertainty in the estimate of mid-puberty for individuals with late pubertal growth. Higher CIs were seen in association with a lower compared with a higher *Pmax*, showing a nonlinear correlation (Figure R10).

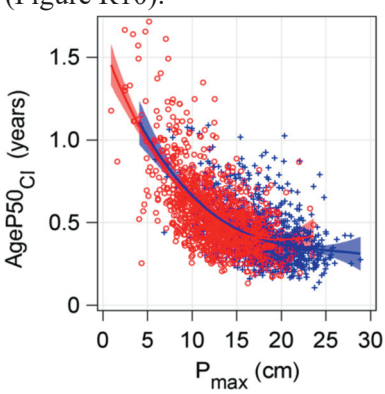


Figure R10. The relationship between the CIs for *AgeP50* and *Pmax* for girls (red circles) and boys (blue crosses). For girls; *AgeP50CI* =1.445 – 0.111 x *Pmax* + 0.00290 x $Pmax^2$, adjusted r^2 = 0.4147. For boys; *AgeP50CI* = 1.278–0.080 x *Pmax* + 0.00171 x $Pmax^2$, adjusted r^2 = 0.2890

CIs were also higher for the onset- and end-estimates of pubertal growth compared with mid-pubertal growth estimates, and in general, CIs were higher in girls than in boys, as seen in Table R3. As expected from the modeling procedure, low *MathSelect* values correspond to a lower maximum CI. *MathSelect* provides a computerised way of selecting individuals with good quality height data.

Table R3 CI for pubertal growth estimates (age in years)

	Girls			Boys		
Variable	**Mean**	**Median**	**SD**	**Mean**	**Median**	**SD**
*AgeTONSET*CI	0.83	0.76	0.33	0.71	0.66	0.24
*AgeP5*CI	0.89	0.80	0.37	0.73	0.67	0.28
*AgeTPHV*CI	0.60	0.54	0.28	0.45	0.41	0.17
*AgeP50*CI	0.54	0.50	0.22	0.43	0.39	0.15
*AgeP95*CI	0.68	0.63	0.25	0.55	0.22	0.60

Values are age in years.

Comments QEPS-puberty study

Estimates for onset, mid, & end of pubertal growth

The QEPS-puberty study presents and explores new measures of pubertal height gain calculated using the QEPS growth model. For the first time, it is possible to automatically calculate estimates for the onset, middle and end of pubertal growth. In 1980, Taranger and Hägg made an ambitious description of different possible measures of pubertal growth; however, their descriptions were based on visual inspection of growth charts, and the measures they proposed were not adopted (186). In the literature, PHV has been widely used as a measure of mid-pubertal growth, and the onset (take-off or nadir) of pubertal growth, based on varying definitions, has also being used in many studies (186, 246, 260, 373, 405, 406). The ICP model used age 2 years before PHV as an estimate for the time of onset of pubertal growth for all individuals in the model fitting process, with no adjustment for sex differences or inter-individual variation (356). It is reasonable to assume that

the precise and individualised way of estimating the onset of puberty offered by the QEPS model, will allow better description of variations in pubertal growth than previous models.

Onset of puberty

When looking at the values of $AgeT_{ONSET}$ and *AgeP1* as measures of the onset of puberty, they suggest an earlier onset than in most other studies. In contrast, *AgeP5* gives an onset of puberty that is generally similar to earlier definitions/calculations (Table R4) (186, 246, 373, 405, 406).

Table R4. Pubertal growth estimates in different studies (age in years)

Variable/study	Girls	Boys
AgeP1 [Paper I]	8.7	10.7
AgeTONSET [Paper I]	9.2	10.7
AgeP5 [Paper I]	9.9	11.8
AgeMHV Zurich [405]	9.8	11.1
AgeMHV London [7]	10.3	12.0
AgeMHV Solna [186]	10.0	12.1
AgeTO Dortmund [246]	8.7	10.3
AgeTO Helsinki [406]	10.1	12.0
AgeTO Copenhagen [260]	10.2	11.8

MHV = minimum height velocity, AgeTO = age at take-off.

The differences between studies may partly be due to secular changes. As the two measures, $AgeT_{ONSET}$ and *AgeP1*, are hard to distinguish visually, and suggest an earlier onset of puberty than most other studies of pubertal height gain, *AgeP5* is considered to be the most suitable measure. Future studies may explore the relationship between the different estimates of onset derived by the QEPS model and the increase in levels of gonadal steroids that defines the onset of puberty from an endocrinological perspective (178, 179).

Mid Puberty

The QEPS model can automatically calculate three new measures of mid-pubertal growth; Age*PPHV*, Age*TPHV* and *AgeP50*. The mean values for all three measures are close to each other. The mean difference in age at midpoint of puberty based on the *AgeP50* measure and age at PHV, as used in the ICP model, was 13 days for boys and 62 days for girls. This suggests that *AgeP50* could be used as a practical measure of mid-puberty.

End of puberty

The end of pubertal growth has widely been neglected in previous studies of pubertal growth patterns, with the exception of the Taranger and Hägg study (186). The QEPS model has three measures that define the end of pubertal growth: *AgeP95*, *AgeP99* and $AgeT_{END}$. These measures may be similar to, but more precise than, the measure *"near adult height"* that is sometimes used in growth research. As with the other measures from the QEPS model, these measures offers defined values that can be calculated automatically. Compared with measures of the onset of pubertal growth or mid-puberty, measures of the end of pubertal growth may be regarded as less clinically important; nevertheless, they are essential for determining the duration of pubertal growth. The duration of pubertal growth is an interesting research subject; topics of interest include investigating secular trends, exploring the impact of different diseases/syndromes on pubertal growth and exploring the impact of very early, very late or deviant growth during puberty on growth and response to growth-promoting treatment.

Adult height & gain in height related to the timing of pubertal growth

Results on timing of pubertal growth and adult height are in agreement with many studies showing that late-maturing individuals are generally taller as adults (187, 371, 379). The relationship between greater adult height and later puberty was apparent for both sexes, in the form of a linear correlation; however, there was wide inter-individual variation, as seen in Figure R8 and the scatterplots published in the QEPS-puberty study (Paper I). The total gain in height during the pubertal years was greater for children with an early compared with a late onset of pubertal growth, confirming previous studies

(186, 361). The reason suggested by the QEPS model for this effect is that early maturing-individuals benefit from more growth related to the higher height velocity of the Q function, which is continuous and declines slowly over time, than late-maturing individuals. *Pmax* was independent of the timing of puberty, as was the P-component in the ICP-model (361). According to this result, is the assumption in the ICP-model with no general differences in the P-component depending on pubertal timing correct, however offers the QEPS model individual variations, not possible with the ICP-model in this respect.

Description of pubertal timing & precision of estimated values by SDS & CIs

An innovation presented in the QEPS-puberty study is the use of individual SDSs and CIs for the measured values. SDSs can be used to relate the measured values of an individual to a reference population. Height SDSs have been widely used in previous growth research and growth charts. The QEPS-model affords the possibility to relate, not just height, but also the pattern of pubertal growth of an individual, to a growth reference and to provide a concise description of the timing of pubertal growth. Since Jim Tanners works in the 1960s and 1970s, individuals have been categorised as having an average, early or late pubertal growth pattern. By providing SDSs, the QEPS-model takes this description to a higher level; the

QEPS-model will show that an individual is, for example, +1.2 or –0.9 years at the time of mid-puberty (AgeP50) related to a reference population (or to the mean of a study group). This description of relative pubertal age also makes it possible to construct growth charts that allow for individualisation in the timing of pubertal growth.

The use of CIs is novel for a growth model; they are of use when validating the quality of the growth data for each individual, as well as when exploring the limitations and reliability of the presented values. The MathSelect function can be used to check the quality of estimated pubertal growth data. Thus, in future, visual inspection of individual data/growth curves could be reserved for outliers and individuals for whom there may be measurement/input errors or too few individual height measurements.

A limitation with QEPS is that the juvenility period, during which some children have accelerated growth velocity, cannot easily be documented by the model. This limitation is however in common with other used growth models describing human growth. Despite this, increased height velocity during juvenility may possibly be visualised as larger residuals from measured values related to the QEPS growth chart and as a higher CI during the months/years of juvenility influence on growth. Another obvious limitation for researchers working with cross-sectional data is that QEPS model longitudinal growth; with pure cross-sectional data can QEPS not be used.

Summary

New measures of pubertal growth from the QEPS-model allows detailed analyses of pubertal growth, and to model individual pubertal growth patterns. The height gained during puberty can be broken down into two components; the height gain due to puberty, resulting from the specific pubertal growth function (P), and the height gain owing to the continuation of childhood growth, resulting from the ongoing actions of the QES-function (continuous growth in height).

AgeP5, *AgeP50* and *AgeP95* representing 5%, 50% and 95% of the specific pubertal growth function, are novel measures for the onset, middle and end of the pubertal growth spurt. The duration of the pubertal growth can be calculated; both individual pubertal height gain and timing can be defined in cm/years and SDSs in relation to the mean. Individual CIs for the pubertal growth estimates can be used to evaluate the reliability of measurements/estimates.

Pubertal height gain due to the P-function is independent of age at onset of puberty; total gain in height during puberty was predominantly due to P-function growth in boys, with less of the gain being related to the QES-function, with the opposite finding for girls. For both sexes, early pubertal growth is associated with greater total height gain during puberty, whereas a late pubertal growth spurt is associated with being taller at adult height.

4.1 PUBERTAL HEIGHT GAIN IN RELATION TO BMI IN CHILDHOOD (PAPER II)

The paper investigates the relationship between height and peak BMI in childhood. In particular, the study investigates how the pubertal pattern of height gain varies in relation to childhood BMI. The QEPS growth model is used for the analyses. Individual longitudinal height data from a subset of children from the GrowUp 1990 Gothenburg cohort are used (1901 individuals with good longitudinal height data). This study will be referred to as the *QEPS-BMI study* in this thesis.

Rationale

Nutritional factors affecting weight in childhood may influence height gain and the timing of puberty. The trends for adult height to increase and puberty to start earlier over time seen during the last 150 years may be related to a parallel increase in weight/BMI during childhood. As the pubertal growth spurt is part of the pubertal transformation, growth during the adolescent years can serve as a proxy for pubertal development. Numerous previous studies have shown an association between high BMI in childhood and early puberty in girls; for boys is the picture more heterogeneous. How the whole pattern of pubertal growth is related to childhood BMI has not been investigated before. The QEPS model is a unique tool for detailed investigation of height gain in general and pubertal growth in particular.

The aim of this study was to investigate in detail how height gain relates to BMI in childhood, using the QEPS growth model. The highest BMI in childhood was assessed relative to growth estimates from the QEPS-model, birth-characteristics and adult height. Due to the rise in weight/BMI observed in girls and sometimes boys in early puberty, an upper age limit for the timing of the highest BMI was set at 7 years of age for girls and 8 years of age for boys. This ensured that the analysis was not biased by data from individuals with a very early onset of puberty. Variables are presented as SDSs for each individual relative to a reference population and also according to different sub groups; children were categorized as underweight

(Uw), average/"normal" (Nw), overweight (Ow) and obese (Ob) based on the highest BMI_{SDS} value recorded (293).

Results

Different BMI-groups in the study population

BMI classification based on highest childhood BMI_{SDS} for the study population of 929 girls and 972 boys is shown in Table R5 (293).

Table R5 BMI-groups according to highest childhood BMI_{SDS}

	Underweight	Normal	Overweight	Obese
Girls	4.1	75.8	16.4	3.7
Boys	2.5	78.0	16.3	3.2

Numbers showing per cent in each sub group.

Pubertal height gain versus childhood BMI

The main finding presented in the *QEPS-BMI study* was an inverse linear correlation across the whole BMI spectrum, between highest childhood BMI_{SDS} and specific pubertal height gain (Figure R11).

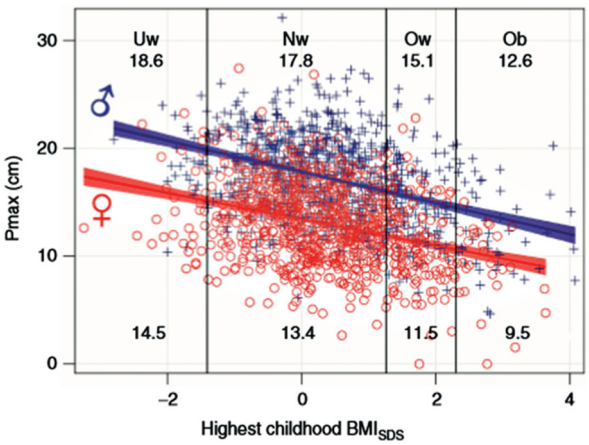


Figure R11. Specific pubertal gain related to peak BMI in childhood. The specific pubertal gain in adult height, *Pmax* is related to the highest BMI_{SDS} for each girl (red circles) and boy (blue cross). BMI_{SDS} for underweight (below −1.51 to −1.29), overweight (above 1.15–1.52) and obesity (2.21–2.30) are marked with approximate vertical lines. Mean values for girls are shown with a red regression line, for boys with a blue regression line, both with shaded areas indicating 95% CI. The mean values of *Pmax* are shown in the bottom (girls) and top (boys). For girls; *Pmax* = 13.66-1.35 x BMI_{SDS}, adjusted r2 = 0.1074. For boys; *Pmax* =18.05-1.61 x BMI_{SDS}, adjusted r^2 = 0.1312. (From paper II, Holmgren et al. Pediatric research. 2017;81:448–54).

The higher the peak BMI between 3.5 and 7 or 8 years of life in girls and boys, respectively, the less was the specific gain in height during puberty. The mean difference between obese and underweight children in the specific pubertal gain (*Pmax*) was 5 cm for girls (range, 9.5–14.5 cm) and 6 cm for boys (range, 12.6–18.6 cm). The pubertal gain from the total growth curve was lower in the OwOb-group than in the NwUw-group, particularly for boys; the difference was smaller than the difference for the specific pubertal gain, 0.9 cm difference in girls and 2.1 cm in boys.

Pubertal timing versus childhood BMI

Onset of pubertal growth, defined as age at 5% of specific pubertal growth, *AgeP5*, for girls/boys was 3.5/2.5 months earlier in the OwOb than the NwUw-group. Mid-puberty, defined as *AgeP50*, was 3.5 and 3.0 months earlier in the OwOb compared with the NwUw group in girls and boys, respectively, and end of pubertal growth (*AgeP95*) was 3.5 months earlier in both sexes in the OwOb compared with the NwUw-group. The duration of pubertal growth was 1 month shorter for the OwOb- compared with the NwUw-boys (Table R6).

Table R6. Pubertal growth estimates (years) related to BMI-groups

	Girls				Boys			
Variable	**LwNw**	**OwOb**	**Difference**	**95% CI**	**LwNw**	**OwOb**	**Difference**	**95% CI**
AgeP5	9.83	9.54	0.29	0.45 –-0.13	11.79	11.58	0.21	0.36 – 0.06
AgeP50	12.06	11.77	0.29	0.45 – 0.13	13.81	13.56	0.25	0.40 – 0.10
AgeP95	14.62	14.33	0.29	0.45 – 0.13	16.11	15.82	0.29	0.44 – 0.14
Duration *AgeP5 – AgeP95*	4.78	4.79	0.004	−0.027– 0.035	4.32	4.24	0.08	0.1 – 0.044

Values showing years for all estimates.

Like the specific pubertal height gain (*Pmax*), the onset of pubertal height gain (*AgeP5*) showed a negative linear correlation with the highest childhood BMI_{SDS} over the entire BMI-spectrum in both sexes, as seen in Figure R12.

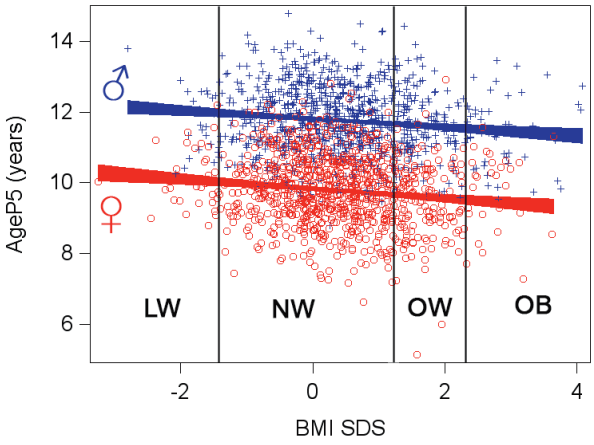


Figure R12. Onset of pubertal growth related to peak BMI in childhood. The onset of pubertal growth, *AgeP5*, plotted relative to the highest BMI_{SDS} for each girl (red circles) and boy (blue cross). BMI_{SDS} for underweight (below −1.51 to −1.29), overweight (above 1.15–1.52) and obese (2.21–2.30) children are marked with approximate vertical lines. Mean values for girls are shown with a red regression line, for boys, with a blue regression line, both with shaded areas indicating95% CI. For girls; *AgeP5* = 13.66-1.35 x BMI_{SDS}, adjusted r2 = 0.107. For boys; *AgeP5* =18.05-1.61 x BMI_{SDS}, adjusted r^2 = 0.131.

Pre pubertal growth and childhood BMI

Already at birth, there were significant differences between children who later became overweight/obese compared with the NwUw group; girls/boys in the ObOw-group were heavier and longer than the NwUw-group. The fetal/infancy exponential component of growth, *Emax*, did not differ between groups (Table R7).

Table R7 Birth weight/length and QEPS growth estimates related to BMI-groups

	Girls			Boys		
Variable	**NwUw**	**OwOb**	**Difference 95% CI**	**NwUw**	**OwOb**	**Difference 95% CI**
Birth weight (g)	3491	3712	221 40 – 494	3638	3760	122 42–201
Birth length (cm)	49.98	50.43	0.45 0.12– 0.78	50.82	51.15	0.33 0.00 – 0.67
Emax (cm)	62.84	62.71	-0.13 -0.59 - +0.33	65.03	65.16	0.13 −0.30 – +0.55
Qmax (cm)	97.77	101.15	3.38 2.14 – 4.63	104.57	108.81	4.24 3.04 – 5.44

Before puberty, children with elevated BMIs were generally taller than NwUw children, and there was a linear correlation between childhood BMI and height at onset of puberty (Figure R13).

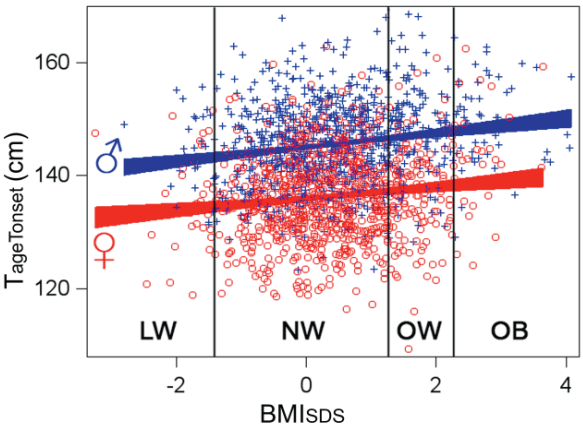


Figure R13. Height at onset of pubertal growth related to peak BMI in childhood. Height at onset of pubertal growth (cm), as height at $AgeT_{ONSET}$ ($TAgeT_{ONSET}$) is related to the highest BMI_{SDS} in childhood for each girl (red circles) and boy (blue cross). Mean values for girls are shown with a red regression line, for boys with a blue regression line, both with shaded areas indicating 95% CI.

Both girls and boys in the OwOb-group experienced more prepubertal growth due to the Q-function than those in the NwUw-group. Q-function growth (*Qmax*) mirrored P-function growth (*Pmax*) and was *positively correlated* with highest BMI in childhood, showing a linear correlation across the entire BMI range (Figure R14). FoU

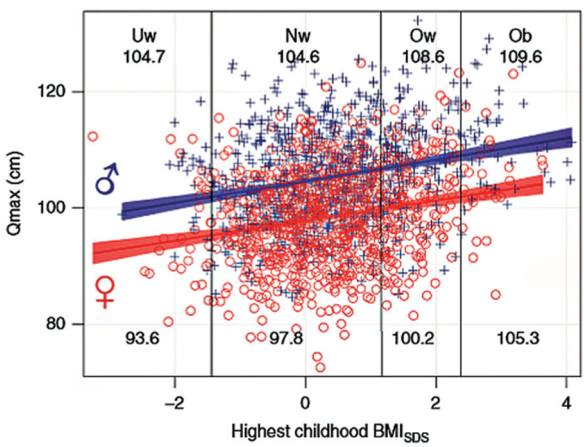


Figure R14. Q-function growth related to peak BMI in childhood. The gain in adult height in cm due to Q-function growth, *Qmax* is related to the highest BMI_{SDS} for each girl (red circles) and boy (blue cross). BMI_{SDS} for underweight (below −1.51 to −1.29), overweight (above 1.15–1.52) and obesity (2.21–2.30) are marked with approximate vertical lines. Mean values for girls are shown with a red regression line, for boys with a blue regression line, both with shaded areas indicating 95% CI. The mean values of *Qmax* are shown in the bottom (girls) and top (boys). For girls; *Qmax* = 97.47 +1.90 x BMI_{SDS}, adjusted r^2 = 0.046. For boys; *Qmax* = 104.32 + 2.02 x BMI_{SDS}, adjusted r^2 = 0.049. (From paper II, Holmgren et al. Pediatric research. 2017;81:448–54).

Balance of P- and QES-gain during puberty related to sex & peak childhood BMI

As seen for the cohort born in 1974 in the *QEPS puberty study*, girls in the *QEPS BMI study* cohort born in 1990 gained more height during puberty owing to the QES- than the P-function, with the reverse being true for boys (Figure R15, Figure R6 for the 1974 cohort). By grouping children according to highest BMI_{SDS} in childhood, it appeared that the balance was shifted towards less P-function-related gain for both girls and boys with higher childhood BMIs, as illustrated in Figure R15.

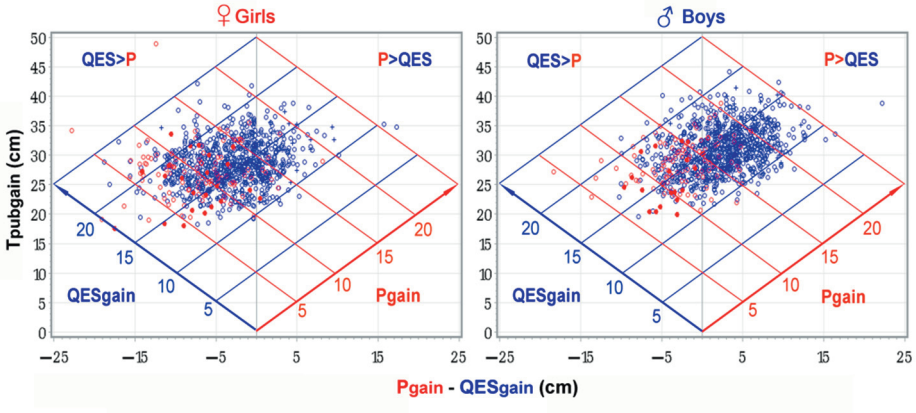


Figure R15. Balance of P- and QES-gain during puberty related to peak BMI in childhood. The Relationship between *Pgain* (= 95% of *Pmax*) and gain from the Q-function during the pubertal years (*QESgain*) showing the total height gain during puberty (T pubertal gain). Relationship is expressed as a subtraction on the horizontal axis (cm) and total pubertal gain (cm) on the vertical axis. If *Pgain* = *QES-gain*, then the difference is zero. Different combinations of *Pgain* and *QESgain* resulting in different total pubertal gain that can be evaluated using the transverse lines for each variable. The oblique blue line, with its transverse blue isolines, represents *QESgain*, and the oblique red line, with its transverse red isolines, represents *Pgain*. For girls (left panel), total pubertal gain depends more on *QESgain* during puberty. For boys (left panel), total pubertal gain depended more on *Pgain* (Figure right). With higher childhood BMI this balance is shifted towards less P-gain for both girls and boys. Blue crosses indicate underweight (Uw), open blue circles indicate normal weight (Nw), red open circles indicate overweight (Ow), red filled circles indicate obesity (Ob). BMI classification according to Cole & Lobstein Pediatric obesity. 2012;7(4):284-94.

Attained heights and adult height versus childhood BMI

Adult height, the total growth function, the sum of (E), Q, P and S, did not differ depending on BMI. Children with high BMI were consistently taller during childhood than children with low/average BMI and gained less height during puberty. As a result, adult height was not related to BMI in childhood. Adult height did not significantly differ between the BMI subgroups for either sex, as seen in Table R8.

Table R8. Adult height related to BMI-subgroups

	Underweight	Normal weight	Overweight	Obese
AH Females	168.0 (38)	168.3 (704)	167.6 (153)	171.3 (34)
AH Males	182.9 (24)	181.6 (758)	182.2 (159)	180.6 (31)

AH = Adult height. Values in cm, in brackets number of individuals in each sub group.

Comments QEPS-BMI study

During the last century, there have been scientific thoughts about how weight and BMI in childhood may affect the timing of puberty and pubertal growth. The *QEPS-BMI study* is the first published investigation exploring in detail the relationship between the pubertal pattern of growth and the highest individual childhood BMI_{SDS}. The QEPS model, previously described in two mainly methodological papers, is for the first time used with a clear clinical objective, serving as a useful tool to investigate pattern of growth related to childhood BMI.

Pubertal height gain and adult height versus childhood BMI

A major finding was the negative linear correlation over the entire BMI range between childhood BMI_{SDS} and specific pubertal height gain (*Pmax*) – the greater the highest BMI in childhood, the less the pubertal gain in height. When looking at total growth during puberty (the more traditional measure), smaller differences were seen between the OwOb and NwUw groups. This was due to the impact of ongoing Q-function growth which is continuous

during both childhood and puberty; the Q-function was positively correlated with BMI in childhood. These results are in line with previous research indicating that less height is gained during puberty in OwOb children compared with their NwUw peers (319, 407).

The linear correlation between the Q-function and peak childhood BMI_{SDS} across the entire BMI range appears to mirror the association between BMI and the P-function, with the combination of P- and Q-function-related growth resulting in adult heights that are independent of BMI in childhood, as seen in other studies (309, 407).

Birth weight/length and early growth versus childhood BMI

Similar to findings in other studies, the *QEPS-BMI study* found correlations between higher birth weight and being overweight/obese in childhood (295, 298). Girls who went on to become overweight or obese were on average 4.5 mm longer at birth than NwUw girls ($p = 0.0085$). Boys who went on to be overweight or obese were 3.3 mm longer at birth compared with NwUw boys ($p = 0.051$). The E-function in the QEPS model do not differ between the two subgroups, hence the differences seen at birth are due to the differences in the Q-function, a mathematical function in the QEPS model that is active from before birth until the attained adult height.

Pubertal timing versus childhood BMI

Another finding confirmed by this study is the association between high BMI and early puberty in girls, which has been reported in numerous other studies (222, 310, 315, 408, 409). The QEPS model enabled detailed investigation of this relationship based on precise estimates; a strong correlation was seen between the highest childhood BMI_{SDS} and early onset pubertal growth. Previous studies on the relationship between the timing of puberty in boys and weight status in childhood have shown conflicting results (246, 309, 310, 315, 319). In the *QEPS-BMI study*, the results for boys are consistent with early puberty being related to higher childhood BMI. OwOb boys enter puberty 2.5 months before NwUw boys, while OwOb girls enter puberty 3.5 months before NwUw girls. The contradictory findings for boys in previous studies may be due to a nonlinear correlation between childhood BMI and

pubertal timing, such that the linear correlation observed within the normal BMI range is lost when obesity is pronounced (410).

Excess calorie intake and being overweight may stimulate linear growth via elevated levels of IGF-I (see chapter 1.7) and diminished hypothalamic inhibition from the pituitary, leading to the start of pulsatile GNRH peaks that initiate puberty (see chapter 1.3) (411, 412). In very obese boys, may this stimulation instead be absent, where elevated levels of estradiol may have an inhibitory effect on gonadotropin secretion affecting the onset of puberty (see chapter 1.7) (184). Thus, the absence of a nonlinear correlation in the *QEPS-BMI study* may be secondary to the limited number of very obese boys in the study group. Another possible explanation for the inconsistent findings regarding BMI and male puberty across different studies could be that the correlation between genital maturation and pubertal height gain is different in obese boys compared with normal weight boys. The findings that obesity in boys is related to late puberty in some studies are generally based on genital maturation, rather than on pubertal height gain (295, 315, 413). It might be that obesity in boys is associated with later genital maturation, however not seen as a later pubertal growth spurt.

So far, only a limited number of obese children (the community based GrowUp study groups), have been analysed by the use of the QEPS model. The pubertal growth in obese children in a clinical setting (University hospital, Madrid) has also recently been analysed by QEPS (414). Preliminary results show similar - albeit not statistically significant - correlations both regarding less pubertal height gain with high childhood BMI and earlier onset of the pubertal growth spurt for both sexes with increasing degrees of obesity. That study group was quite small, (47 individuals with accurate growth data from birth to adult height) and further studies would be interesting to attain more insights for the relations of childhood obesity and the pubertal pattern of growth.

An innovative feature of the QEPS model is that it is possible to define the duration of pubertal growth based on estimates for the onset and end of the pubertal growth spurt. A previous study found an association between high BMI in juvenility and a shorter duration from onset of the pubertal growth spurt to PHV, for both boys and girls (246). One possible theory is that the pubertal growth process is accelerated in Ow/Ob children; accelerated

pubertal growth was seen for boys, with the duration of pubertal growth being 1 month shorter in Ow/Ob boys compared with their Nw/Uw counterparts. An explanation for why this was not seen in girls in the *QEPS-BMI study* could be that earlier puberty in girls is associated with a slower pace of progression (415), and that these two mechanisms cancel each other out.

Summary

Childhood BMI is an important factor for subsequent height gain.

In both sexes, peak BMI during childhood correlates positively with height gain before the onset of pubertal growth and with an earlier onset of the pubertal growth spurt. Both of these linear correlations hold true over the entire BMI spectrum.

Peak childhood BMI correlates negatively with growth arising from the specific pubertal growth function (P) in the QEPS model in both sexes. The higher the BMI, the less the height gain during puberty. This negative linear correlation is present over the entire BMI spectrum.

The ongoing Q- (QES) function in the QEPS model that continues throughout childhood and puberty correlates positively with peak childhood BMI. This relationship mirrors the relationship between the P-function and BMI. Thus, the P- and Q-functions cancel each other out, resulting in adult heights that are independent of peak BMI in childhood.

4.2 SECULAR CHANGES IN HEIGHT IN THE NORDIC COUNTRIES (PAPER III)

The paper is a comparative study of how height has changed during the last four decades in the Nordic countries; Denmark, Finland, Norway and Sweden. The study looks at changes in attained adult height over time and explores the contributions of the different growth periods to these changes. The Swedish studies of Solna 1956 study and the GrowUp Gothenburg 1974 and 1990 cohorts also captured data on the height of parents of study participants, meaning that trends in adult height over seven decades could be analysed. This study is referred to as the *Nordic height study* in this thesis

Rationale

Over the last 100-150 years, a trend for adult height to increase over time has been reported in developed countries. It has been referred to as a positive secular trend, and associated with better health, improved socioeconomic development and socioeconomic equality (2, 3). As attained adult height is the sum of growth in utero, during infancy, childhood and puberty, changes in any one of these growth phases could be responsible for increasing adult height. Furthermore, the growth phase in which the change occurs that leads to a greater adult height may vary over time and between populations (4, 7). In previous research, secular trends in adult height have been attributed mainly to increased height in infancy and early childhood (4-6). However, in parallel with the secular trend in height, there is also a trend for earlier puberty over time. All Nordic countries except for Iceland and Sweden have published updated national growth references in the last 7 years, and a new growth reference for Sweden based on the GrowUp 1990 cohort, is coming soon (11-13). In most cases, there are approximately four decades between the current and the previous growth reference. In the Swedish 1956, 1974 and 1990 growth studies, information on the heights of parents of participants were also available. Hence, there is a scope to compare changes in height over the last four decades in most Nordic countries, and over the last seven decades in Sweden. Other aims of the analysis were to evaluate during which

growth periods the changes occur, and to evaluate whether the trend for earlier pubertal growth is ongoing in the Nordic countries.

Results

Attained adult heights in the Nordic countries

There was a positive secular trend with increased adult height during the last four decades in Denmark, Finland, Norway and Sweden, as shown in Figure R16. Adult height increased by 6 mm/decade for females (Norway 4 mm, Sweden 6 mm, Finland/Denmark 7 mm), and 9 mm/decade for males (Sweden 5 mm, Finland 7mm, Denmark 8mm, Norway, 15 mm). For Norway, adult height was based on height at 16.9 years of age in the old reference and 18 years in the new reference. If height at 17 years of age was compared for these populations, the change in height was +3 and +10 mm/decade for females and males, respectively.

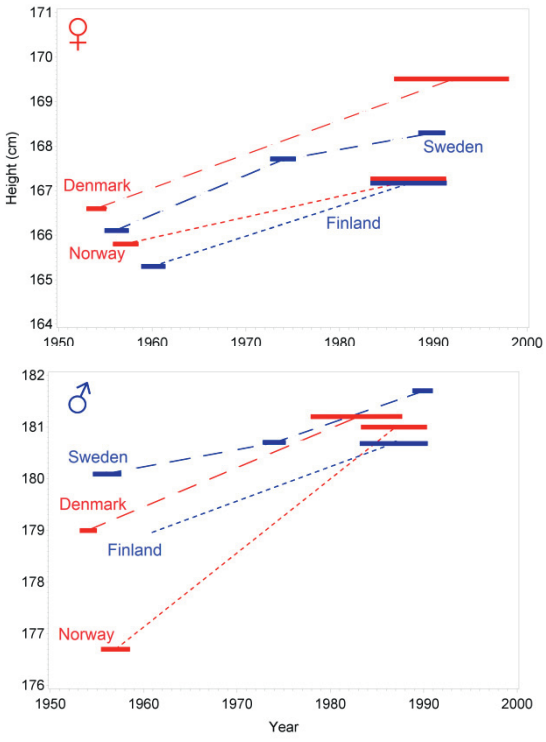


Figure R16. Adult height in Nordic growth studies. Mean adult height of females (upper panel) and males (lower panel) in seven Nordic growth studies. The horizontal lines indicate birth year. Danish heights are based on females/males born 1953–1954 and females/males born 1987–1998/1978–1988. Finnish heights are based on individuals born 1959 1961 and 1983–1991. Norwegian heights are based on height at 16.9 years for individuals born 1956–1958, and at 18 years of age for individuals born 1983–1991. Swedish heights are based on the Solna 1956, GrowUp 1974 and 1990 Gothenburg cohorts.

Numerical values of attained adult heights in the Nordic countries are presented in Table R9.

Table R9. Attained adult heights (AH) in the Nordic growth studies

	Females		Males		
Country Year of Birth	**AH (cm)**	**Age (year)**	**AH (cm)**	**Age (year)**	**Paper**
DENMARK					
1952-1965	166.6	18	179.0	18	Andersen[212]
1977-2002	169.5	18	181.2	20	Tinggaard[211]
FINLAND					
1959-1971	165.3	18	178.9	20	Sorva[369]
1983-2009	167.2	20	180.7	20	Saari[386]
NORWAY					
1956-1968	165.8	16.9	176.6	16.9	Waaler[209]
1983-2006	167.2	19	181.0	19	Juliusson[388]
	166.6	17	179.7	17	
SWEDEN					
1956	165.4	18	178.5	18	Karlberg[168]
	166.1	25	180.1	25	Hägg[363]
1974	167.7	18	180.7	18	Paper II
1981	167.0	19	180.4	19	Werner[384]
1990	168.3	17-20	181.7	17-21	Paper II

Adult heights of participants in the Swedish 1956, 1974 & 1990 growth studies and their parents

There was a continuous increase in height from the older to the younger generation in comparisons of adult heights of study participants and their parents in the Swedish 1956/1974/1990 growth studies. (Figure R17). The only exception was that fathers in the GrowUp 1990 Gothenburg cohort were taller than male participants in the 1974 cohort. The greatest increase in height over time was seen between the parents of the growth cohort born in 1956 and the parents of the 1974 cohort, with a difference of 30 mm for fathers and 28 mm for mothers. This equates to an increase in height of 17 mm/decade for fathers and 16 mm/decade for mothers (1956-1974).

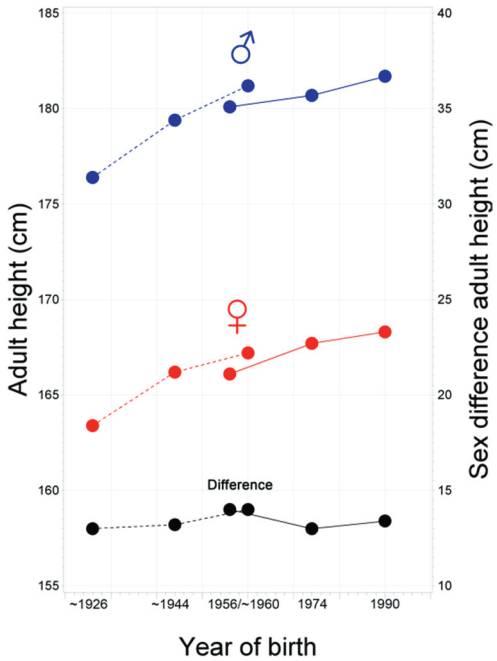


Figure R17. Adult height of participants and parents in Swedish growth studies. Mean adult heights in cm of individuals participating in the Swedish 1956, 1974 and 1990 growth studies together with the mean heights of their parents. For the 1956 cohort, raw data on parental heights were not available within the publication, so this analysis was based on the mean values reported (parents were measured). For the 1974 and 1990 cohorts, individual heights of parents were available (from questionnaires).

The parents of participants in the Swedish GrowUp 1990 cohort were also taller than the parents of those in the 1974 cohort; mothers by 8 mm (5 mm/decade) and fathers by 15 mm (9 mm/decade). Females in the GrowUp 1974 and 1990 Gothenburg cohorts were taller as adults than their mothers by 13 and 11 mm, respectively. Males in the 1974 and 1990 cohorts were taller as adults than their fathers by 10 and 5 mm, respectively.

Differences in attained height at different ages

Differences in attained length/height between the oldest and the most recent growth study for each age in each country are shown in Figure R18.

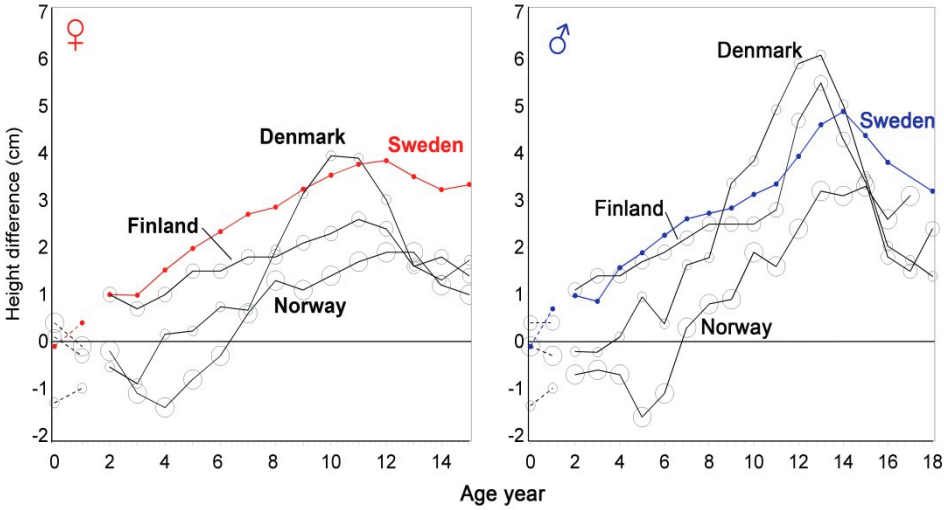


Figure R18.. Changes in heights. Mean differences in attained length/height (in cm) between the most recent and previous growth reference within the different Nordic countries. Swedish data were based on the Solna 1956 growth study and the GrowUp 1990 Gothenburg growth study. For Denmark, Finland and Norway the former and present national growth references were compared.

Attained length/height at 0 to 8 years of age

Variations in birth-length were 49.6 to 50.9 cm for girls and 50.2 to 51.5 cm for boys. The difference in attained lengths at birth ranged from –13 to +6 mm for both girls and boys (Table R10). Attained length at 1 year, and height at 2 years, was greater in the most recent Swedish and Finnish cohort compared with the previous cohorts. In Denmark and Norway, 1–2 year old infants/toddlers were consistently shorter in the most recent cohort than in the previous one. Height for girls/boys at 4, 6 and 8 years of age was generally greater in the more recent cohorts than in the earlier cohorts with the exception of Norway, with height at 4 and 6 years being lower for both sexes in the most recent compared with the earlier cohort.

Table R10. Attained lengths/heights (cm) at 0-8 years in the Nordic growth studies

A. Girls

Country Year of Birth	BL cm	1y	2y	4y	6y	8y	Paper
DENMARK							
1952-1965	50.9	76.0	87.1 S	103.5	117.2	128.1	Andersen[212]
1977-2002	49.6	75.0	86.5 S	103.7	117.9	130.0	Tinggaard[211]
FINLAND							
1959-1971	50.2	74.8	86.2 S 87.7 L	102.5	116.0	128.3	Sorva[368, 369]
1983-2009	50.3	74.9	87.2 S 88.7 L	103.5	117.5	130.1	Saari[386]
NORWAY							
1956-1968	50.0	- 75.3	- 86.9 S	- 104.0	117.3	128.5	Waaler[209] Knudtzon[387]
1983-2006	50.4	75.2	86.7 M	102.6	117.0	129.8	Juliusson[388]
SWEDEN							
1956	50.2	75.2	86.0 S 87.5 L	102.2	115.6	127.4	Karlberg[168]
1974	49.9	74.7	86.8 S	103.4	117.5	129.7	Paper IV
1981	50.1	74.8	87.0 S	103.7	118.1	130.1	Werner[384]
1990	50.1	75.6	87.0 S	103.7	117.9	130.3	Paper IV

B. Boys

Country Year of Birth	BL cm	1y	2y	4y	6y	8y	Paper
DENMARK							
1952-1965	51.5	78.0	88.5 S	104.7	118.8	129.0	Andersen[212]
1977-2002	50.2	77.0	88.3 S	104.7	119.2	131.8	Tinggaard[211]
FINLAND							
1959-1971	50.7	74.2	87.7 S 88.1 L	103.3	116.8	129.0	Sorva[368, 369]
1983-2009	50.1	74.6	88.8 S 89.3 L	104.7	118.7	131.5	Saari[386]
NORWAY							
1956-1968	50.8	- 77.0	- 88.2S	- 104.7	118.7	130.0	Waaler[209] Knudtzon[387]
1983-2006	50.7	76.7	87.5 M	104.0	117.6	130.8	Juliusson[388]
SWEDEN							
1956	51.0	76.4	87.3 S 88.9 L	103.1	116.6	128.6	Karlberg[168]
1974	50.5	76.2	87.9S	104.2	118.2	130.5	PaperIV
1981	51.0	76.3	87.8S	104.6	118.4	130.8	Werner[384]
1990	50.9	77.1	88.3	104.7	118.9	131.3	Paper IV

Measurements at 2 years; BL = baseline, S = standing, L = supine, M= values obtained through smoothing standing and supine measurements.

Attained height at 10 to 18 years of age

For boys, height at 10 years of age represents childhood growth; at this age, height was greater in the most recent growth studies compared to earlier cohorts. The greatest increase was noticed in Denmark (39 mm) and the smallest in Norway (19 mm), as seen in Figure R18 and Table R11. Due to earlier puberty in girls than boys, will height at 10 years of age in girls be influenced by pubertal growth. Height attained at 10 years of age in girls was greater in more recent cohorts than in earlier cohorts in all four countries (from +14 mm in Norway to + 40 mm in Denmark). For both sexes, height at 12 and 15 years of age was greater in the most recent growth study compared with the oldest in each country. In all countries, differences in height between the older and more recent cohorts were greatest at 10–12 years in females and 12–15 years in males.

Table R11. Attained heights at 10-25 years in the Nordic growth studies

A. Girls

Country Year of Birth	10y cm	12y cm	15y cm	AH cm	Age year	Paper
DENMARK						
1952-1965	138.4	150.4	163.1	166.6	18	Andersen[212]
1977-2002	142.1	153.4	164.8	169.5	18	Tinggaard[211]
FINLAND						
1959-1971[*1]	139.5	151.4	162.8	165.3	18	Sorva[369]
1983-2009[*2]	141.8	154.0	164.2	167.2	20	Saari[386]
NORWAY						
1956-1968	139.1	151.4	164.5	165.8	16.9	Waaler[209]
1983-2006	140.5	153.3	165.5	167.2 166.6	19 17	Juliusson[388]
SWEDEN						
1956	138.2	150.9	163.2	165.4	18	Karlberg[168]
				166.1	25	Hägg[363]
1974	141.0	153.9	165.8	167.7	18	Paper IV
1981	141.5	154.7	165.6	167.0	19	Werner[384]
1990	141.7	154.8	166.5	168.3	17-20	Paper IV

AH = adult height.

B. Boys

Country Year of Birth	10y cm	12y cm	15y cm	AH cm	Age year	Paper
DENMARK						
1952-1965	139.1	148.8	168.3	179.0	18	Andersen[212]
1977-2002	143.0	154.7	171.8	181.2	20	Tinggaard[211]
FINLAND						
1959-1971	139.8	150.0	168.4	178.9	20	Sorva[369]
1983-2009	142.2	154.3	171.8	180.7	20	Saari[386]
NORWAY						
1956-1968	139.7	150.4	169.9	176.6	16.9	Waaler[209]
1983-2006	141.6	152.8	173.2	181.0 179.7	19 17	Juliusson[388]
SWEDEN						
1956	139.1	149.3	170.1	178.5	18	Karlberg[168]
				180.1	25	Hägg[363]
1974	141.3	152.1	173.3	180.7	18	Paper IV
1981	141.8	152.6	172.9	180.4	19	Werner[384]
1990	142.2	153.2	174.5	181.7	17-21	Paper IV

AH = adult height.

Comments Nordic height study

Adults becoming taller over time in the Nordic countries

The *Nordic height study* showed that there is still a continuing secular trend for adult height to increase over time in both females and males in the Nordic countries. The change is about the same magnitude in the different countries, 4–7 mm/decade for females and 5–8 mm/decade for males, with the exception of Norway in which the increase in males is greater. This is most likely owing to the fact that adult height measurements were taken at a younger age in the population used in the old compared with the new Norwegian reference, meaning that the magnitude of the trend for Norwegian males was exaggerated. The results also show that the *relative position* of

adult height within the Nordic countries (tallest females in Denmark, tallest males in Sweden) are unchanged for both sexes in all four countries with the exception of males in Norway.

Comparisons of parental heights in the Swedish 1956, 1974 and 1990 growth studies were consistent with the positive secular trend, and extend the time period investigated to seven decades. Analysis of parental heights shows that the magnitude of increases in height is declining; the greatest differences in height were seen between the parents of the 1956 (born in the 1920s to early 1930s) and 1974 (born in the mid-1940s) cohorts. Two unexpected observations were that fathers of individuals in the 1974 birth cohort were taller than males in the 1956 birth cohort, and that fathers in the 1990 cohort (born on average around 1960) were taller than male subjects in the 1974 cohort (born approximately 14 years later). Reasons could be that parental heights in the 1974/1990 cohorts were overestimated owing to the fact that they were self-reported (416), or because men who go on to be fathers are generally taller than males who do not go on to have children (52). The fact that the parents of participants in the 1956 cohort were measured by a study team and that the measures reported in the 1974 cohort were self-reported, may indicate that the secular trend for the adult height of the parents to increase from the 1920s to the 1960s is slightly overestimated.

Attained heights at different ages – when does the increase in height occur?

The variations in birth-length and the difference in length/height at 1 and 2 years of age between countries are inconsistent; there were no clear common findings in the four countries investigated. These results are however in agreement with other research concerning secular changes in height during the first years of life, which also show a highly heterogeneous picture (221, 222, 224, 417, 418).

The gain in height during the pre-pubertal years was greater in more recent compared with earlier cohorts; however, the pace was different in the different countries. The increase in height is apparent at an earlier age in Finland than in other countries, with the next earliest increase in height being in Sweden, followed by Denmark and then Norway. One reason why the increase in height during childhood appears latest in Norway may be the

lower prevalence of obesity and/or being overweight (lower BMI values during childhood) in the most recent Norwegian cohort compared with the most recent cohorts in other Nordic countries (404). This is in analogy with the results of the *QEPS-BMI study*, where higher childhood BMI were related with taller heights during childhood. The observation that cohorts born more recently are taller during childhood than earlier-born cohorts/generations is in line with previous research on secular changes during the second half of the 20th century (see chapter 1.5 for details) (221, 222, 224, 419). In all countries studied, height gain during the early and mid-pubertal years was greater for both sexes in cohorts used in the most recent compared with the earliest growth studies. Differences in height during the early/mid adolescence were more pronounced than those in the late adolescence and/or at adult height, indicating a left-shifted pubertal growth spurt. Thus, the *Nordic height study* showed not only a trend for adult height to increase over time, but also a common trend of earlier puberty. The finding are in line with most other studies, although there is evidence that the trend for earlier pubertal timing may level off in some countries (189, 221, 224, 256, 260, 310, 420, 421).

Methodological aspects

The *Nordic height study* may raise some methodological questions. Ideally, a comparative study like this should be based on different studies, and should include studies using common designs and definitions. However, there are several differences between the growth studies analysed. The Swedish studies were longitudinal, whereas the studies from the other Nordic countries were semi-longitudinal, cross sectional, or included mixed study groups. No common definitions of adult height were used, and most of the measurements were performed in WBC and school health care settings; only measurements in the Swedish 1956 study and the final measurement(s) in the GrowUp studies were made by a trained study team. The criteria for study inclusion and exclusion were similar. In all but one case, the populations used to develop growth references did not include individuals with an ethnic background outside the Nordic countries; Finland was the only exception, and immigrants made up only a small proportion of the study population. Infants with low birth weight and children with chronic diseases were excluded in all studies.

It is possible that the differences between studies result in a slight underestimation of adult height, at least for males, in Denmark, Finland and Norway. On the other hand, the study settings for the growth studies conducted at different time points were consistent within countries, meaning that the changes over time within countries are reliable (with the exception of for males in Norway, as mentioned previously). To compare growth during the adolescent years using cross sectional/semi-longitudinal and longitudinal study groups may pose a methodological problem. Technically, however, it is possible to calculate PHV based on modelled cross-sectional data on mean or median height, although the resulting calculations should be interpreted with great caution as they are not precise. For this reason, we have not included such calculations in this study. However, the positive secular changes observed, in terms of adult height, height during childhood and the timing of mid-pubertal growth over time in all countries investigated, indicate the validity of the conclusions in a broader sense.

Summary

In four Nordic countries, Denmark, Finland, Norway, and Sweden, the positive secular trend for adult height is ongoing, with height increasing by 4–8 mm/decade for females and by 5–15 mm/decade for males based on analysis of date on individuals born from the 1950s to 1990s.

By studying height in parents of participants in three Swedish growth studies, it was shown that parental heights also increased over time, with height increasing by 11 mm/decade for mothers and by 14 mm/decade for fathers born from the 1920s to 1960s.

The increases in height occurred mainly during the childhood growth phase.

There is an ongoing secular change with earlier timing of pubertal growth over time in the Nordic countries.

4.3 SECULAR CHANGES IN GROWTH PATTERNS (PAPER IV)

The manuscript presents an in-depth analysis evaluating changes in growth patterns from birth to adult height in two Swedish population-based cohorts born in 1974 and 1990. With use of the QEPS model and these two similar growth cohorts from the same geographical area born 16 years apart, even small changes in growth patterns can be detected. Differences between the populations can be analyzed by exploring how the underlying growth functions from the QEPS model have changed or are related. This study referred to as the *Growth pattern study* in this thesis.

Rationale

The pattern of human growth is characterized by periods of acceleration and deceleration. The total increase in height can be divided into phases; the fetal growth period before birth, the rapid and rapidly declining infancy growth period, the childhood period with long-term linear growth, and the pubertal spurt growth, extending until adult height is attained. Variations in the timing and amplitude of the growth functions generate different growth patterns. Growth patterns differ between sexes, populations, and over time. Changes over time are known as secular changes; increases in height with time are considered a positive secular change. Knowledge of these changes in a population is important, both for the scientific understanding of human growth, and in the development of relevant growth references for detecting deviations in growth in children, that can be markers of diseases or psychosocial problems. A growth model can be a tool for studying the underlying changes between two study cohorts, and the QEPS model offers a unique tool for studying changes in different growth periods/growth functions. The aim of this study was to use the QEPS model to evaluate changes in growth functions in two Swedish cohorts born in 1974 and 1990.

Results

The E-function & early growth/characteristics at birth

The E-function and the first part of the Q-function in the QEPS model delineate growth in uteri and during infancy. Comparisons of the tempo of early growth (*Etimescale*) and the gain in adult height due to E-function growth (*Emax*) showed that growth during the fetal and infancy period was more rapid in the cohort born in 1990 than in the 1974 cohort. A significantly shorter *Etimescale* was seen in the 1990 versus 1974 cohort for both girls and boys, while the total E-function growth (*Emax*) was similar in both cohorts (Table R12). Consistent with this result, boys born in 1990 were longer at birth than boys born in 1974. Girls and boys born in 1990 were also significantly heavier at birth, than those born in 1974. These increases were apparent despite the fact that children in the 1990-born cohort were younger at birth than the 1974-born cohort based on gestational age (GA).

Table R12 Comparison of early growth characteristics for girls and boys in the 1974 and 1990 growth cohorts

Variable Girls	1974 (N=1139)	95% CI	1990 (N=929)	95% CI	Difference	p-value (t-test)
Emax	62.9	62.7-63.0	62.8	62.6-63.0	-0.05	0.69
Etimescale	1.02	1.01-1.02	1.00	0.99-1.00	-0.02	<0.001
Weight	3405	3378-3432	3536	3503-3568	131	<0.001
Birth length	49.9	49.8-50.0	50.1	50.0-50.2	0.17	0.061
GA	282.1	281.6-282.6	281.2	280.6-281.8	-0.9	0.002
Boys	(N=1141)		(N=972)			
Emax	65.1	64.9-65.2	65.1	64.9-65.2	-0.02	0.88
Etimescale	1.00	1.00-1.01	0.98	0.98-0.99	-0.02	<0.001
Weight	3513	3485-3541	3662	3630-3694	149	<0.001
Birth length	50.5	50.4-50.6	50.9	50.7-51.0	0.37	<0.001
GA (days)	281.4	281.0-281.8	280.9	280.3-281.4	-0.5	0.05

GA = gestational age (days), Emax and birth length in cm, weight in gram.

More E-function-related growth was attained by the time of birth in the 1990 cohort compared with the 1974 cohort, and the decline in height velocity of E-function growth was more pronounced in the 1990 cohort due to the faster *E-timescale* (Figure R19). The total height gain related to the E-function was

significantly greater in the 1990 relative to the 1974 cohort until 0.9 years of age in girls and 1.1 years of age in boys, as seen in Figure R19.

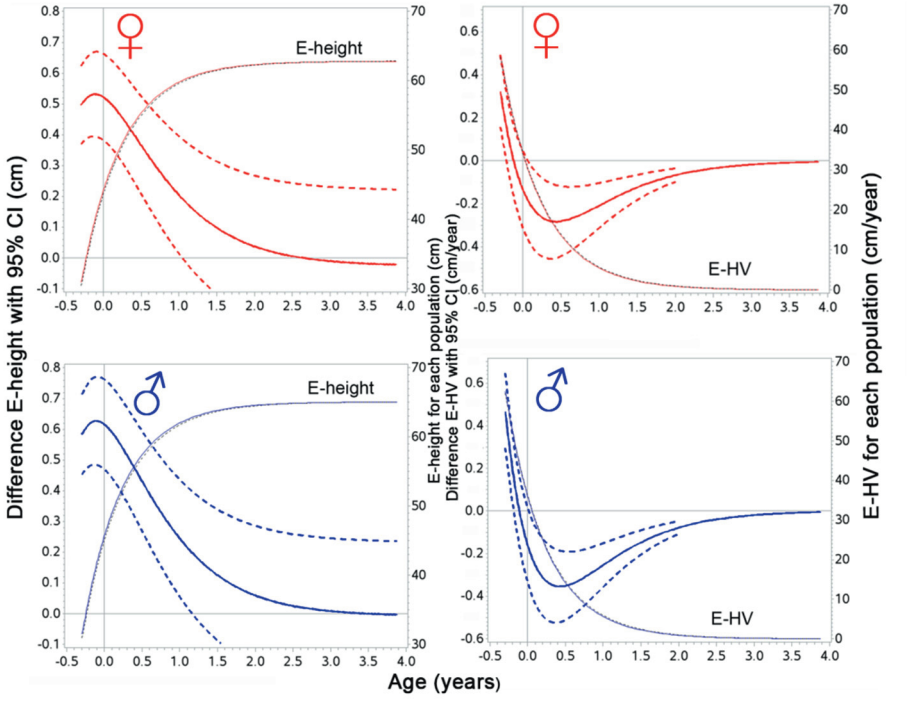


Figure R19. Difference in E-function. Left panel: Difference in attained E-function-related height gain between 1990 and 1974 cohorts together with the corresponding total mean E-function-related height gain for girls (top) boys (bottom). The bold dotted lines show the 95% CI of the difference between the cohorts. The thin solid lines show the mean E-function-related height gain of the 1990 cohort, and the thin dotted lines show the mean E-function-related height gain of the 1974 cohort. **Right panel:** Difference in E-function-related height velocity between 1990 and 1974 study cohorts together with the corresponding mean E-function-related height velocity for girls (top) and boys (bottom). The dotted lines show the 95% CI of the difference; there is a significant difference between the cohorts when this CI is not overlapping zero on the x-axis. The thin solid lines show the E-function-related height velocity of the 1990 cohort, and the thin dotted lines show the E-function-related height velocity of the 1974 cohort.

The Q-function & growth during childhood

During childhood, the Q-function describes an increase in height (the Q-function is active from before birth through the pubertal period until adult height is reached). *Qmax*, together with total height at 4, 6, and 8 years of age was compared to study differences between the populations in childhood growth. Increases in height due to the Q-function growth were greater for girls and boys in the 1990 cohort than for girls and boys in the 1974 cohort, with differences being most pronounced for boys, as seen in Tables R13. Boys in the 1990 cohort were taller than boys in the 1974 cohort between the ages of 2 and 8 years. For girls, the difference in Q-function was less marked, resulting in a borderline significant increase at 4 years of age (p = 0.07) and significantly increased height at 6 and 8 years of age in the 1990 relative to the 1974 cohort (Table R13).

Table R13 Comparison of Q-function & heights (cm) at 2 to 8 years of age for girls & boys in the 1974 & 1990 growth cohorts

Variable Girls	1974 (N=1139)	95% CI	1990 (N=929)	95% CI	Difference	p-value (t-test)
Qmax	97.6	97.2-98.0	98.4	97.9-99.0	0.85	0.013
Height 2 y	86.8	86.6-87.0	87.0	86.8-87.2	0.21	0.103
Height 4 y	103.4	103.2-103.6	103.7	103.5-103.9	0.29	0.072
Height 6 y	117.5	117.3-117.8	117.9	117.7-118.2	0.41	0.041
Height 8 y	129.7	129.4-130.0	130.3	130.0-130.6	0.52	0.026
Boys	(N=1141)		(N=972)			
Qmax	104.0	103.6-104.5	105.4	104.9-105.9	1.35	<0.001
Height 2 y	87.9	87.8-88.1	88.3	88.1-88.5	0.35	0.006
Height 4 y	104.2	104.0-104.4	104.7	104.4-104.9	0.49	0.002
Height 6 y	118.2	117.9-118.5	118.9	118.6-119.1	0.66	<0.001
Height 8 y	130.5	130.2-130.8	131.3	131.0-131.6	0.81	<0.001

Y = years

Q-function growth for both sexes in the two cohorts is visualised in Figure R20.

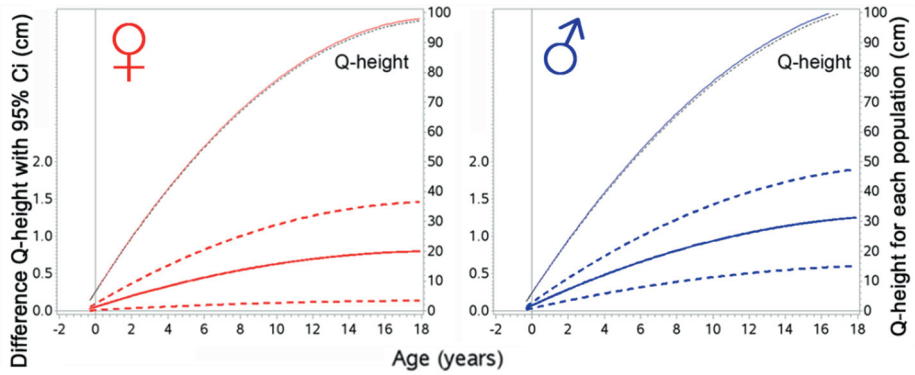


Figure R20. Difference in Q-function. Difference in Q-function related height attained between the 1990 and 1974 cohorts, together with the corresponding total mean Q-function related height for girls (left) boys (right). The bold dotted lines show the 95% CI of the difference. The thin solid lines show the mean Q-function related height of the 1990 cohort, and the thin dotted lines show the mean Q-function related height of the 1974 cohort. The dotted lines show the 95% CI of the difference between the cohorts.; there is a significant difference between the cohorts when this CI is not overlapping zero on the x-axis.

The P-function, growth during puberty & adult height

During puberty, the P-function describes specific pubertal height gain and, since the P-function has a tempo estimate, the *Ptimescale* in the QEPS model, different P-estimates (as time for *AgeP5* and *Ptimescale*) can also be used to determine the timing and duration of pubertal growth. For girls, pubertal growth was about 1 month earlier in the 1990 cohort than in the 1974 cohort based on mid (*AgeP50*) and end (*AgeP95*) estimates of pubertal growth. For boys, there were no significant changes in the timing of pubertal growth, with the exception that boys in the 1990 cohort reached *AgeP95* 1 month earlier than the 1974 cohort (Table R14).

Table R14 Comparison of pubertal growth & adult height for both sexes in the 1974 & 1990 growth cohorts

Variable Girls	1974 (N=1139)	95% CI	1990 (N=929)	95% CI	Difference	p-value (t-test)
AgeP5	9.86	9.80-9.91	9.78	9.71-9.84	-0.08	0.056
AgeP50	12.09	12.03-12.15	12.00	11.93-12.06	-0.09	0.032
AgeP95	14.66	14.61-14.72	14.56	14.49-14.62	-0.10	0.017
Duration P5-P95	4.80	4.79-4.81	4.78	4.77-4.80	-0.02	0.027
Pmax (cm)	12.8	12.6-13.0	13.0	12.7-13.2	0.19	0.247
Total pub. gain	26.3	26.1-26.6	26.8	26.5-27.0	0.42	0.011
Adult height	167.7	167.3-168.0	168.3	167.9-168.7	0.62	0.023
Boys	(N=1141)		(N=972)			
AgeP5	11.78	11.72-11.83	11.75	11.69-11.81	-0.03	0.518
AgeP50	13.80	13.74-13.85	13.76	13.70-13.82	-0.03	0.408
AgeP95	14.66	14.61-14.72	14.56	14.49-14.62	-0.10	0.017
Duration P5-P95	16.10	16.04-16.15	16.05	16.00-16.11	-0.04	0.307
Pmax (cm)	17.3	17.1-17.6	17.2	17.0-17.4	-0.15	0.340
Total pub. gain	29.0	28.8-29.2	29.1	28.8-29.3	0.06	0.701
Adult height	180.7	180.3-181.1	181.7	181.3-182.1	0.99	<0.001

All Age estimates in years, gain and adult height in cm.

The gain in adult height from the specific P-function (*Pmax*) did not differ between the two cohorts, neither for girls nor boys. Since the total growth during puberty is a combination of Q and P-functions, the total height gain during puberty (*Tpubgain*) was greater in girls from the 1990 compared with the 1974 cohort. The duration of pubertal growth was significantly shorter for girls (but not boys) in the 1990 compared with the 1974 cohort (about seven days). The resulting adult height was greater in the later-born cohort for both sexes; for girls due both to growth during puberty and childhood, for boys due mainly to increased growth during childhood (higher Q-function). Differences in the P-function between the 1974 and 1990 cohorts are also shown in Figure R21.

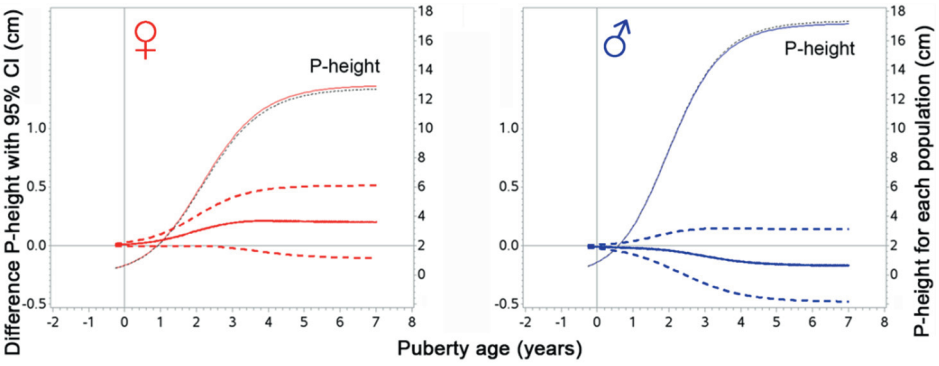


Figure R21. Difference in P-height function height between 1990 and 1974 cohorts together with the corresponding total mean P-height for girls (left) boys (right). The bold dotted lines show the 95% CI of the difference. The thin solid lines show the mean P-height of the 1990 cohort, and the thin dotted lines show the mean P-height of the 1974 cohort. The dotted lines show the 95% CI of the difference; there is a significant difference between the cohorts when this CI is not overlapping zero on the x-axis. Age is adjusted for onset of puberty, meaning that differences in the timing of puberty are not visualized.

Differences between the 1974 and 1990 cohorts in the total gain (that is, in the total QEPS function) for both height and height velocity, are seen in Figure R22.

For both sexes, height was greater in the later-born cohort at all ages, except for in girls during early childhood, where the CI of the difference in height between 2 and 5 years of age just overlapped zero, as indicated by the lower dotted line. For both sexes, attained height was significantly greater during the pubertal years in the later-born cohort; however, total QEPS function height velocity during puberty was not significantly different between the two cohorts.

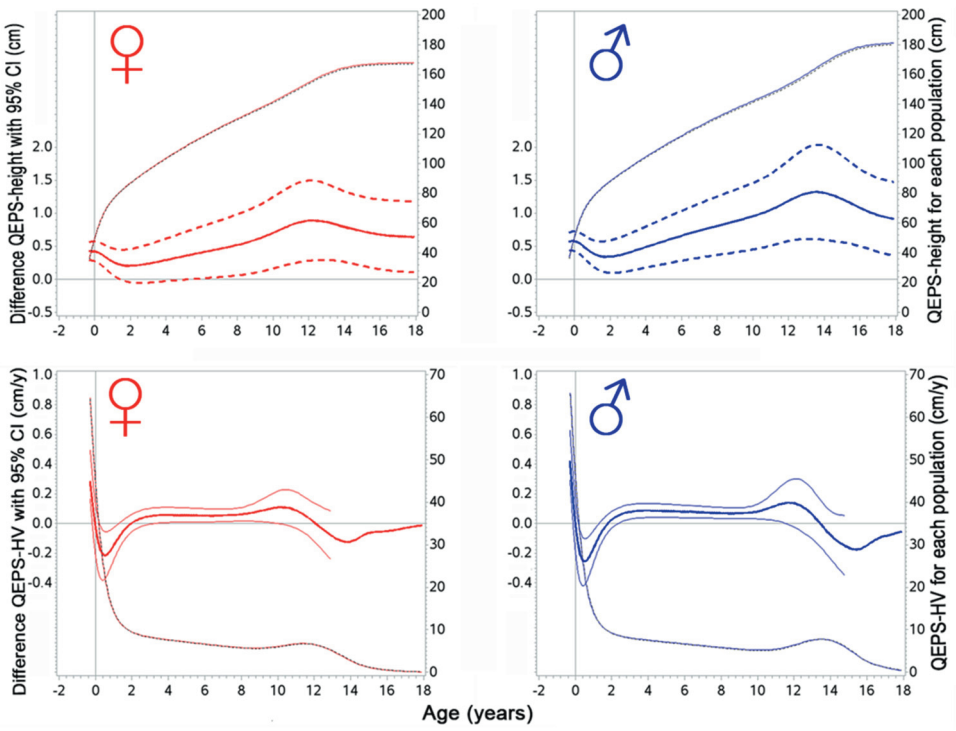


Figure R22. Upper panel: Difference in attained QEPS height between 1990 and 1974 study cohorts together with the corresponding mean total QEPS height for females (left) and males (right) . The dotted lines show the 95% CI of the difference between the cohorts. The thin solid lines show the mean QEPS height of the 1990 cohort, and the thin dotted lines show the mean QEPS height of the 1974 cohort. **Lower panel:** Difference in QEPS-height velocity between 1990 and 1974 study cohorts together with corresponding mean total QEPS-height velocity for females (left) and males (right) . The thin lines show the 95% CI of the difference between the cohorts. The thin solid lines show the mean QEPS-height velocity of the 1990 cohort, and the thin dotted lines show the mean QEPS-height velocity of the 1974 cohort

Comments Growth pattern study

The QEPS model as a tool to detect changes in growth patterns

The *Growth pattern study* illustrates that the QEPS model is a useful tool to identify differences in growth patterns between two longitudinal growth cohorts born only 16 years apart. By deconstructing the growth curve to reveal the underlying functions in the QEPS model, insight are provided as to

why individuals born in 1990 are on average taller as adults than those born in 1974. The increased growth observed for males in the 1990 compared with the 1974 cohort is mainly a result of greater Q-function growth; females in the later-born cohort were taller as adults due to undergoing more growth during both childhood and puberty than the earlier-born cohort.

Growth during infancy & childhood (E & Q-functions)

From the QEPS model, the first difference between the cohorts seen is a significantly faster *Etimescale* in the 1990 compared with the 1974 cohort. A faster *Etimescale* reflects the tempo of the E-function, meaning that *Emax* is reached earlier. These findings are in parallel with the increases in weight and length at birth seen in the later born cohort, although these findings were only borderline significant for females (2 mm longer newborn girls, p=0.06 in the 1990 versus 1974 cohort). The changes observed occur despite the fact that GA at birth is 0.5–1.0 days shorter in the 1990 cohort. Better circumstances in utero, with improved antenatal care and less maternal smoking during pregnancy, are potential reasons for the differences (417, 422). Higher birth weights in the later-born cohort are also in line with the greater adult height in the 1990 cohort; previous studies have shown correlations between heavier birthweight and taller height in adulthood (423, 424). With the QEPS model, does this parallel a higher Q-function as the Q-function in the model runs from before birth until attained adult height. Higher birth weights in the more recently born cohort are also in agreement with previous Nordic studies reporting a rise in birth weight over time (417, 418, 425).

The finding of greater length at birth in the later-born cohort is, however, not in line with the results in the *Nordic height study* that showed a heterogeneous pattern. A former Danish study also found a heterogeneous picture with *decreased* length at birth measured in 1973–1983 and *increased* length when measured a decade later in 1983–1993 (418). It could be that small differences in length and GA at birth may be the result of methodological differences between studies (see chapter 1.7) and so these data should be interpreted with caution.

A faster *Etimescale* equates to a faster tempo of infancy/early childhood growth with an earlier transition from infancy to childhood (ICT) growth in the ICP model (100, 378, 426). Early ICT is associated with taller adult

height (100, 426), as is confirmed by the results of the *Growth pattern study*, with faster *Etimescale* and taller adult height for both sexes in the later-born cohort.

The finding of greater attained height during childhood in the 1990 compared to the 1974 cohort is also in line with previous research on secular trends (221, 222, 224, 231, 402, 404, 419), and can be attributed to the higher Q-function (*Qmax*) in the later-born cohort. These results are also consistent with the secular trend in the Nordic countries (with the exception of Norway) for individuals to be becoming taller during childhood over time shown in the *Nordic height study*. The fact that the changes are statistical significant later in childhood for girls compared with boys is due to that the Q-function is a continuous variable, with a smaller increase in *Qmax* in girls than boys between the two cohorts. The finding in the *QEPS BMI study* that higher childhood BMI is associated with higher *Qmax* is likely to explain the increased Q-function in the later-born cohort in this study. We observed that BMI was increased in the 1990 compared with the 1974 cohort, especially in boys (398).

Pubertal growth & adult height (P & total QEPS-functions)

Regarding the pubertal pattern of growth, girls in the later-born cohort started puberty about 1 month earlier than girls in the earlier-born cohort, while for boys there was no significant differences in timing between cohorts. The results are consistent with other studies on secular changes where girls in particular have entered puberty earlier over time, while more heterogeneous results have been seen for boys (189, 224, 255, 256, 260, 419-421). Compared with the differences between the Swedish 1956 and 1974 cohorts (where PHV decreased by 0.4–0.5 years for both sexes); however, it appears that the secular trend for earlier onset of pubertal growth has slowed down for Swedish females and ended in Swedish males. The total QEPS-function showed higher values at all ages for children in the 1990 versus the 1974 cohort; equating to greater height (except borderline significance in girls 2–5 years) in the later-born cohort, resulting in this group being taller at adult height. Females in the later-born cohort were 6 mm taller at adult height than those in the earlier-born cohort; the gain was owing to a 2–4 mm increase during childhood and about 4 mm during puberty. The discrepancy between the sum of the components and the total difference in adult height is due to

the earlier pubertal growth that curtails 1–2 mm of the childhood height gain in the 1990 cohort. Males in the 1990 cohort were 10 mm taller as adults compared with males in the 1974 cohort, which was due to increased growth during childhood.

Summary

There is a positive secular trend for adult height to increase in Sweden when comparing the adult heights in the GrowUp Gothenburg 1974 and 1990 cohorts.

The greater adult height in the 1990 cohort is due to more growth during childhood in both sexes, and during puberty for girls.

The progressively earlier timing of puberty during the last 150 years seems to have leveled off in Swedish girls and ended in Swedish boys.

The QEPS model was effective at detecting small changes in growth patterns, in two longitudinal growth cohorts born only 16 years apart.

5 GENERAL DISCUSSION

The research reported in this thesis contributes to the understanding of human growth patterns in several ways. The four papers that form this thesis each add information that helps us to gain a better understanding of growth patterns and the factors that influence growth. The two main achievements of the *QEPS-puberty study* were (1) to characterise the pattern of growth during puberty precisely and in more detail than possible in previous studies, and (2) to illustrate how different patterns of pubertal growth is seen in a healthy population. The results provide a tool for future growth research. The *QEPS-BMI study*, shows for the first time that for both sexes there is a linear relationship between BMI in childhood and both the timing of pubertal growth and the height gained during puberty; this relationship spans the entire BMI range. These findings have implications for everyday clinical evaluations of growth as part of routine school health care and in paediatric/adolescent outpatient clinics.

In the *Nordic Height study*, the positive secular trend in adult height (previously known) is shown to be continuing and is similar in the four investigated Nordic countries. This study is the first to illustrate a secular change in height in three generations of parents and children. Increased growth during mainly childhood contributes to the positive secular change in adult height and the timing of pubertal growth is earlier for both sexes in all investigated Nordic countries in the most recent growth reference populations. The conclusions from the *Nordic height study* may be of interest beyond the scientific community, for the public in the Nordic countries. The focus of the *Growth pattern study* is to investigate how short-term secular changes in growth (over a 16-year period) can be modelled by the functions of the QEPS model. The study shows that there is an ongoing positive secular trend in adult height in Sweden; underlying this pattern, height gain during childhood continues to increase, while the secular trend for an earlier onset of pubertal growth is now levelling off. The findings of this study illustrate that QEPS is a sharp instrument for describing changes in growth, as well as highlighting the benefits of using longitudinal data when modelling growth.

Why do we see secular changes in height patterns and attained adult heights? Clearly, genetics alone cannot be the answer to this question, given that the changes in height observed have been impressive over only a few generations. Changes in circumstances during infancy and childhood that impact positively on factors such as nutrition, psychosocial wellbeing and diseases are likely to be of importance. In particular, the intake of protein (quantity and type) during infancy and childhood may play a role; milk and animal proteins being linked to more growth than wheat proteins (209). Changes in nutrition are reflected in BMI; thus, changes in BMI during childhood may be the common denominator underlying the results of the *QEPS-BMI study*, the *Growth pattern study* and the *Nordic height study*. Epigenetic mechanisms are also likely to be of importance; it is possible that changes in nutrition during infancy and childhood in one generation can affect growth patterns in the next generation through epigenetic mechanisms (427).

As noted in the introduction, there is no general common definition of *growth patterns* in humans. The growth pattern or growth trajectory of the individual is the change in height (amplitude) over time (tempo) from birth to adult height. Growth can be seen as a journey, where the end of the journey (adult height) may be the same, although the path is different. To explore the journey in detail, it is essential to have longitudinal data for each individual. Growth patterns can also be viewed at the group level, with the distribution of a growth variable in a group, as seen in the many scatterplots in this thesis. The QEPS-model elegantly describes both the individual and grouped growth patterns. As Groucho Marx said, "*Those are my principles, and if you don't like them... well, I have others".* My interpretation of this quote in the current setting is that the QEPS model can describe many types of growth pattern, regardless of which definition of growth pattern is being used.

The *QEPS-puberty study* has contributed to existing research by showing new, innovative measures of the pubertal growth spurt generated by the QEPS model. Pubertal height gain can be seen both as the specific pubertal gain (P-function) – what puberty adds to the ongoing continuous growth (Q-function) – and in more traditional terms as the total gain in height during the pubertal years (Q+P). No previous studies have described and explored pubertal growth in this amount of detail. This is partly because previous growth models have not included both an ongoing growth function and a

specific pubertal growth function that can truly be individualised. Although the ICP model uses a specific pubertal function, the function is fixed, meaning that pubertal height gain cannot be fully individualised. Using data from the QEPS model, it is possible to model and describe individual patterns in both total and specific height gain during puberty. By showing a lot of scatterplots of the different pubertal growth estimates from the QEPS-model, the *QEPS-puberty study* visualises all different individual variants, clearly showing that individual patterns in both total and specific height gain during puberty exist, can be modeled, and can be described. The individualised specific pubertal growth is essential in both modelling growth during puberty as close to the "real" individual pattern as possible and for studying the underlying mechanisms of pubertal growth (Figure I.2).

In order to model growth as realistically as possible, the QEPS model includes both estimates similar to those identified visually in earlier studies, as well as new estimates. The new measures for onset of pubertal growth (*AgeTonset* from the total growth, *AgeP5* and *AgeP1* from the specific P-function) correspond to what can be visualized by the eye; the point at which height velocity increases and the pubertal growth spurt begins. These estimates are analogous to previously used descriptions/measures such as nadir, onset, and take-off. The mid-pubertal growth estimates (*TPHV* from the total growth, *PPHV* and *AgeP50* from the specific P-function), are also similar to the previously used measure of PHV. In contrast, the end estimates (*AgeTend* from the total growth, *AgeP95* and *AgeP99* from the specific P-function) have almost no equivalents in previous research, despite being prerequisites for calculating the duration of pubertal growth, and providing a more precise measure of pubertal height gain. However, the end estimates are consistent with the onset estimates, making them intuitive to use. Thus, clinicians and researchers working with adolescent growth may easily understand the principles underlying the QEPS model estimates.

As a consequence of the *QEPS-puberty study*, computer based puberty adjusted growth references (for height/weight/BMI), can now be constructed for clinical use allowing individualisation of growth evaluation during the adolescent years (399). (Figure R9).

This new tool may be of significant value for monitoring growth in adolescents undergoing puberty earlier or later than expected based on the

average of their peers. Until now only references for pre pubertal individual growth have been used (Figure I.31). The tools for computer based puberty adjusted growth references, allowing for individualised evaluation of growth during the adolescent years are at hand, the more concrete development can now take place.

One of the most striking advantages of the new measures from the QEPS model is that they are generated automatically by the mathematical functions underlying the model. This means that growth data can be analysed in an efficient way without the need for time-consuming assessments of each individual growth curve; this also minimises the risk of human estimation errors. Methodologically, investigating how the frequency and distribution of measurements affect the modelling of individual growth by QEPS remains to be fully elucidated.

In future, the QEPS model can be used to explore the factors and mechanisms underlying different growth patterns. Exploration of the changes associated with puberty has been limited to date. It would be of interest to use the QEPS model to explore in detail the relationships between the hormonal changes during puberty and the changes in growth and development of secondary sexual characteristics. We know that both the amplitude (levels) and tempo (rhythm of secretion) of GH, testosterone and estradiol change with biological maturation/puberty; now it is possible to study the interplay between hormones, secondary sexual characteristics and growth pattern using QEPS estimates (Figure GD1).

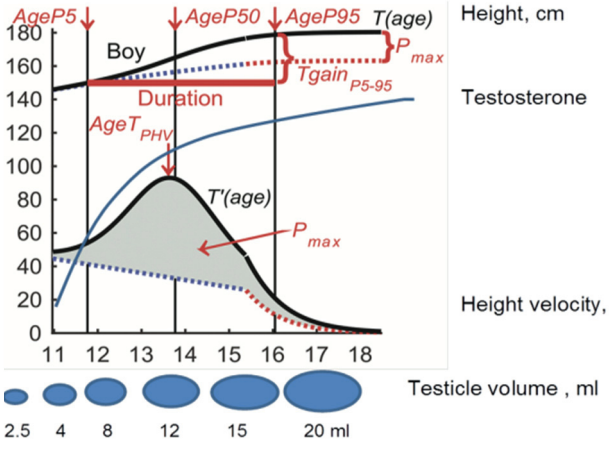


Figure GD1. The three ways of defining puberty. In boys, schematic figure.

The three ways defining puberty (hormones/pubertal maturation/growth patterns) also may be linked to BMI/body composition. There is potential for these investigations to increase our understanding of normal physiology, as well as our understanding of pathophysiology and the impact of treatments. It is also anticipated that the growth functions and growth patterns characterised by QEPS may be related to genes, hormone; rhythms, levels, and tissue sensitivity/receptor expression, as well as to post-receptor events.

The most novel finding in the *QEPS-BMI study* was the negative linear correlation of childhood BMI and the specific pubertal height gain. This result scientifically confirms both indirect findings from previous research and a clinical intuition of how overweight/obese children often grow. The other main result, that higher BMI in childhood was related to earlier puberty in both sexes is confirmative regarding females to results of previous studies, whereas for males it is a new finding; an evidence in the scientific debate weather high BMI in childhood is linked to early or late puberty in boys. The results explain the tendency to overestimate future height gain in overweight or obese children, and are therefore useful for those conducting clinical assessments of growth and trying to predict adult height in individual children. Secondary sex characteristics have been used as markers of puberty in previous research into weight status/BMI and pubertal timing. It would now be of interest to follow longitudinal growth patterns and the development of secondary sexual characteristics in children grouped according to BMI during infancy and/or childhood. A better understanding of these relationships may shed light on the reasons for reports of a variable relationship between timing of pubertal growth and weight status in boys. Another topic for the future may be to study the relationship between growth patterns described by the QEPS model and other measures of weight status/adiposity, such as waist-circumference, bio- or multi-electrical impedance, DXA-measures or MRI evaluations.

The *Nordic height study* and the *Growth pattern study* remind us that growth is a dynamic process, not just at the individual level, but also over time, at the population level. The results from studies presented in this thesis show that, contrary to expectations, the positive secular trend for adult height has not ended in the tall populations of Northern Europe, at least not in Nordic populations. The four Nordic countries studied in this body of research have similar cultures, historic and ethnic backgrounds, as well as economic and

social circumstances; maybe unsurprisingly, the secular changes observed were also similar. However, it is important to remember that these populations are all relatively tall, with children being longer/taller in infancy and childhood in comparison with many other countries.

The opinion of WHO regarding a universal growth reference (that all healthy children are supposed to grow similarly) is based on a sympathetic idea; however, the assumption may instead be counterproductive in populations with taller stature during infancy, childhood and puberty. The use of the WHO growth reference in taller than average populations will lead to fewer short children with possible diseases/psycho-social problems being detected. As positive secular changes may occur in more countries owing to improvements in diet and living conditions, any universal growth reference may also quickly become outdated (428). These changes mean that having population- or country-specific growth references will be important over the next decades. The QEPS model have the option to be a useful tool to investigate different sub-groups and populations since the underlying growth functions are described with precise estimates. In research, the QEPS model hence can be used as a common "reference", whereas longitudinal data is a prerequisite for the evaluations.

The secular changes reported in previous studies have often been related to changes over several decades or even longer periods. Thus, it may be considered surprising to focus on secular changes of a time span of only 16 years. The *Growth pattern study* shows that it is possible to discuss secular changes over a short time period and that even different growth periods can be analysed. The QEPS model offers this possibility. When investigating different parts of the growth trajectory (growth phases) with relatively small changes it is very important that there are no systematic differences between the study groups. Obviously, the composition of the study groups (inclusion criteria, socio-economics, and ethnicity) needs to be similar. Measurements techniques, and even the time of the day for the measurements may also be important if the differences are quite small. When comparing changes over a longer time-period (with more pronounced changes in growth patterns), close similarity between study groups is not that critical.

The progressively earlier timing of mid-puberty observed over the last century in affluent societies seems in Sweden to have slowed down in girls

and leveled off in boys as revealed by pubertal growth estimates from the QEPS model. It may appear contradictory related to the results from the *Nordic height study*, with a general trend for earlier pubertal growth for both sexes in all countries. However, the comparisons in the *Nordic height study* for Sweden were made between individuals born 1956 and 1990. During these 34 years the trend has been observed, when looking only at the last 16 years in the *Growth pattern study*, the picture partly changed.

To date, studies using the QEPS model have explored total growth, with more in-depth analyses focusing on describing the pubertal pattern of growth in detail (published in three papers; the first QEPS model paper in the appendix, the *QEPS puberty* study and *QEPS-BMI study* in this thesis). Only one study has so far looked at growth during infancy and childhood (the *Growth pattern study*). In the future, it would be interesting to conduct an in-depth analysis of growth patterns during infancy and early childhood in order to better understand the mechanisms for delayed growth during this growth phase. Hypothesising that delayed ICT by the QEPS model will be seen as a longer E-timescale and maybe also a lower Q-function, whereas a faster E-timescale could be linked to high protein intake. Nutrition and psychosocial factors during infancy/early childhood are likely to be related to such growth patterns, possible to study with the QEPS model. Since the QEPS model describes growth with different individual height scales (E and Q) and time-scales (E), both amplitude and tempo, together with SDS and CI, QEPS provides a more detailed picture of early growth compared to the ICP model, describing when the transition between infancy and childhood occurs.

Concepts of *optimal growth*, height that has reached the *genetic potential*, or the *saturation of a secular change* in height, has earlier been discussed; these notions may be part of a much more complex picture. With evolutionary perspectives, growth patterns have different trade-offs, a certain growth pattern may be optimal for some situations or beneficial regarding risks for some diseases and negative in other situations and risks of other diseases. The genetic and epigenetic background of an individual may have an impact; a preferable pattern of growth for one child may not be optimal for a child with another genetic/epigenetic background. To get more insights of beneficial growth patterns, longitudinally followed children for growth measurements together with sampling for biochemical/biological markers and

hormones and information of health and diseases in a life-course perspective will be needed.

The last decade of GWAS (genome wide association studies) has found many genes associated with different traits. These studies have been hypothesis free; results have been generated like trawling for fish. In research ahead, not just big GWAS will give answers; another way could be to identify individuals/families with similar growth patterns and in these more selected cases search for genes. In this setting, QEPS can be used to identify and specify growth patterns in a more targeted search for genes, to use a harpoon instead of a trawl, explaining the genetic component of variations in growth patterns.

6 CONCLUSION

This thesis shows how novel estimates of pubertal growth from the QEPS model make it possible to conduct more detailed analyses of pubertal growth than ever before. Relationships between childhood BMI_{SDS} and pubertal growth are shown, and secular changes in growth during the last four decades in the Nordic countries were analysed, together with a more detailed analysis of growth patterns in two Swedish longitudinal growth cohorts. The more specific conclusions, answering the specific aims are described below.

1a. New variables for estimating the onset, middle and end of pubertal growth were explored which provide measures of both the duration of the pubertal growth spurt and height gain during puberty. Growth during puberty could be described by a combination of specific P-function growth and growth related to the continuing QES-function. QEPS is the first growth model that expresses the timing (age) and amount (cm) of pubertal growth in individual SDS. All pubertal estimates were described with individual CIs for the first time, defining objective criteria for evaluating data reliability. *This means that pubertal growth for the first time automatically can be modelled and analysed with defined estimates for timing and height gain, a significant contribution to research concerning growth during the adolescent years.*

1.b. The specific height gain during puberty (P-function) was found to be independent of age at onset of the pubertal growth spurt, whereas the total height gain during puberty, including that owing to the ongoing QES-function, was greater in individuals starting pubertal growth early (both sexes). Late onset of pubertal growth correlated with higher adult height. A sex difference was also seen, with more QES-function growth in girls than boys during puberty. *These findings were in line with most previous research, validating that the QEPS model in an appropriate way can model growth during puberty.*

2.a and 2.b Childhood BMI_{SDS} was inversely associated with pubertal height gain as a linear correlation across the entire BMI range, adding new knowledge of BMI in childhood and subsequent growth. Substantially more pre-pubertal growth (Q-function) was seen in children with higher childhood BMI_{SDS}. Due to diminished P-function growth in individuals with higher

BMI_{SDS}, these two functions (Q-growth and P-growth) cancel each other out, and the resulting adult height is independent of BMI_{SDS} in childhood. In both girls and boys, a higher childhood BMI_{SDS} is associated with an earlier onset of pubertal growth. *These results are consistent with findings from other researchers regarding girls and give more evidence that similar results are valid also in boys, a matter of controversy in current research regarding pubertal timing.*

3.a and 3.b The Nordic countries show a positive secular change, with taller adult heights for both sexes during the last four decades. This is shown separately for each country before; whereas the present study, compare the countries and find similar patterns. All countries investigated had earlier pubertal growth in the most recent growth reference compared to the oldest reference. Increased height gain during childhood underlies a majority of the increase in adult height observed in the most recently studied populations. Information on parental heights in Swedish cohorts shows a stronger secular trend in adult height during the earlier three-decade period, extending the studied period to approximately 70 years. *This is not previously studied in a longitudinal setting.*

4. In the detailed comparisons of growth patterns (individuals born around 1974 and 1990, respectively), the conclusion was that there is a still ongoing trend for length/height to increase from birth to adulthood in Swedish boys and girls. Height gain during childhood was responsible for the positive change in adult height in both sexes, and more height gain during puberty was also seen for girls in the later born cohort. *The secular change for a progressively earlier onset of pubertal growth has slowed in girls and leveled off in boys, a novel finding. The study adds new insight to previous research of secular changes, that by use of the QEPS model, changes in a relative short time period can be analysed in a longitudinal setting, from birth to attained adult height.*

7 FUTURE PERSPECTIVES

In the general discussion, I have outlined several important paths for future research, now possible due to the results presented in this thesis. Analysing early growth, by the E- and Q-functions from the QEPS model, related to nutrition and psychosocial factors is one possible topic, to study "the three ways defining puberty" with the interplay between hormones, genital maturation and growth patterns another. Investigations of growth functions from QEPS/growth patterns linked to body composition, DEXA- and MRI-evaluations for better understanding of obesity and the other extreme anorexia are other options, as well as methodological studies concerning measurement frequency and development of tools like growth references aligned for individual timing of puberty.

Further analyses of data obtained from the GrowUp 1974 and 1990 Gothenburg cohorts could look at the relationships between growth patterns and health/disease, lifestyle (diet, sleep, physical activity), body perception, well-being, and ethnic origin. With several Swedish national registries, based on unique national identity numbers, there is also a possibility to study growth patterns related to health, disease and socioeconomic factors in a life course perspective in future research.

This research project started with curiosity about whether children have or not have similar patterns of growth as their parents –an intergenerational growth project. The project followed another path and the collection of essential background information for performing an intergenerational growth study ended up in this thesis. With the new tools and knowledge derived from these studies, the table is now set for comparisons of growth patterns between generations to be made during infancy, childhood and puberty.

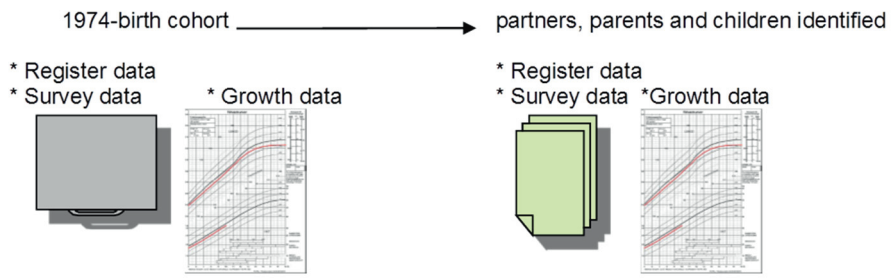


Figure FP 1. Intergenerational growth study. Collection of archived growth data.

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Research is not a one man (or woman!) show. In clinical research and in studies like the ones in this thesis, on healthy children and adolescents, the work is based on confidence, trust and willingness to contribute to the public's best, characterizing an open and democratic society.

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