DISSERTATIONS IN
HEALTH SCIENCES

Antti Saari

Modern methods for auxological screening of growth disorders in children

Publications of the University of Eastern Finland
Dissertations in Health Sciences

UNIVERSITY OF
EASTERN FINLAND

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To be presented by permission of the Faculty of Health Sciences, University of Eastern Finland for public examination in Auditorium 2, Kuopio University Hospital, Kuopio, on Saturday, March 28th 2015, at 12 noon

Publications of the University of Eastern Finland
Dissertations in Health Sciences
Number 274

Department of Pediatrics
Institute of Clinical Medicine, School of Medicine,
Faculty of Health Sciences,
University of Eastern Finland
Kuopio
2015

Kopio Niini OY
Helsinki, 2015

Distributor:
University of Eastern Finland
Kuopio Campus Library
P.O.Box 1627
FI-70211 Kuopio, Finland
http://www.uef.fi/kirjasto

ISBN (print): 978-952-61-1722-5
ISBN (pdf): 978-952-61-1723-2
ISSN (print): 1798-5706
ISSN (pdf): 1798-5714
ISSN-L: 1798-5706

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Saari, Antti
Modern methods for auxological screening of growth disorders in children
University of Eastern Finland, Faculty of Health Sciences
Publications of the University of Eastern Finland. Dissertations in Health Sciences 274. 2015. 93 p.

ISBN (print): 978-952-61-1722-5
ISBN (pdf): 978-952-61-1723-2
ISSN (print): 1798-5706
ISSN (pdf): 1798-5714
ISSN-L: 1798-5706

ABSTRACT

Growth monitoring is a fundamental part of preventive child health care since it aims for early detection of childhood illnesses. This screening process relies on important tools such as up-to-date growth reference curves, evidence-based screening cut-off values for abnormal growth, and accurate diagnostic procedures for early detection of growth disorders. The general aim of this thesis was to create new, evidence-based tools for auxological screening of growth disorders in children.

Due to secular change in growth in children, growth references have to be up-dated periodically. The first part of this thesis consisted of the collection of contemporary auxological data from over 72,000 healthy children born between 1983 and 2009 which was then used to calculate new Finnish growth reference values. On average, Finnish children were found to be growing taller than children in the former Finnish growth reference (born 1956 – 1973). The mean adult height of Finnish boys and girls had increased from 178.9 to 180.7 cm (+1.8 cm), and 165.6 to 167.5 cm (+1.9 cm), respectively.

In the second part of this thesis, screening of growth disorders in up-to-date national growth references was shown to outperform World Health Organization's (WHO) recently published multiethnic growth curves. Screening cut-off value at specificity 99% detected 55% of Turner syndrome (TS) girls when the new Finnish growth references were used as opposed to only a 20% detection rate with the WHO curves.

In this study, evidence-based cut-off limits for attained height, weight and growth rate were developed, and these were validated against two target conditions: Turner syndrome (TS) and celiac disease (CD). Earlier detection of both conditions can be facilitated with systematic growth monitoring, and screening accuracy was found to be excellent [area under receiver operating characteristics curve (AUC ROC) = 0.99] for TS girls, and good (AUC ROC = 0.88 for girls and 0.84 for boys) for CD when several growth parameters were used simultaneously.

The adoption of electronic health records provides an alternative to develop automated growth monitoring programs. In this study, the effectiveness of automated growth monitoring program was found to be distinctly better than its manually orientated counterpart in primary care. The automated strategy improved the detection rate of growth disorders by 6 – 7 -fold. It also identified numerous children with a growth disorder who would previously have been missed with the standard growth monitoring.

Modern methods for growth monitoring in children are now ready for implementation in the healthcare system. Evidence-based growth monitoring program could be carried out accurately with these methods permitting the early detection of growth disorders in primary care.

National Library of Medicine Classification: WS 103, WS 104, WS 141, WB 286, WX 175, QS 677, WD 175
Medical Subject Headings: Body Height; Body Mass Index; Body Weight; Celiac Disease; Child; Electronic Health Records; Growth Charts; Growth Disorders; Mass Screening; Sensitivity and Specificity; Turner Syndrome

Saari, Antti
Lasten kasvun seurannan uudistaminen Suomessa
Itä-Suomen yliopisto, terveystieteiden tiedekunta
Publications of the University of Eastern Finland. Dissertations in Health Sciences 274. 2015. 93 s.

ISBN (print): 978-952-61-1722-5
ISBN (pdf): 978-952-61-1723-2
ISSN (print): 1798-5706
ISSN (pdf): 1798-5714
ISSN-L: 1798-5706

TIIVISTELMÄ

Kasvun seuranta on tärkeä osa lasten ehkäisevää terveydenhuoltoa. Sen tarkoituksena on tunnistaa aikaisessa vaiheessa kasvuun vaikuttavia sairauksia jo ennen muita sairauden oireita. Toimivan kasvun seurantajärjestelmän osat ovat ajantasaiset kasvukäyrät, tutkimusnäyttöön perustuvat kasvun seulontasäännöt ja hyvät diagnostiset menettelyt kasvusairauksien tunnistamiseksi. Tämän väitöskirjan tavoitteena oli uudistaa kasvusairauksien seulontaa Suomessa.

Lapsilla on ollut taipumus kasvaa vanhempiaan pidemmiksi aikuisiksi, minkä vuoksi kasvukäyrät tulee uudistaa säännöllisesti. Väitöskirjan ensimmäisessä osatyössä kerättiin yli 72 000 tervettä lasta (syntyneet 1983 – 2009) sisältävä kasvuaineisto, jonka avulla laadittiin uudet kasvukäyrät suomalaisille lapsille. Nykylasten havaittiin kasvavan keskimäärin aiempaa noin 40 vuotta vanhan kasvukäyräaineiston lapsia (syntyneet 1956 – 1976) pidempinä. Poikien aikuispituus oli lisääntynyt 178.9 cm:stä 180.7 cm:iin (+1.8 cm) ja tyttöjen 165.6 cm:stä 167.5 cm:iin (+1.9 cm).

Väitöskirjan toisessa osatyössä osoitettiin, että kasvuun vaikuttava sairaus voi jäädä tunnistamatta, jos käyttäisimme monikansallisia Maailman terveysjärjestön WHO:n -kasvukäyriä ajantasaisten kansallisten kasvukäyrien tilalla Suomessa. Kansallisia kasvukäyriä käyttämällä Turnerin oireyhtymää sairastavista tytöistä 55 % jäi kiinni kasvuseulonnassa kahteen ikävuoteen mennessä, kun jatkotutkimuksiin poimittiin yksi prosentti terveistä lapsista. Vastaavasti vain 20 % tytöistä jäi kiinni WHO-käyrillä.

Väitöskirjan kolmannessa ja neljännessä osatyössä laadittiin tutkimusnäyttöön perustuvat määrittelyt lasten poikkeavalle pituudelle, painolle ja kasvussa tapahtuville muutoksille. Turnerin oireyhtymää ja keliakiaa käytettiin tutkimuksissa mallisairauksina. Systemaattinen kasvuseulonta voi auttaa molempien sairauksien aikaisessa tunnistamisessa. Turnerin oireyhtymä oli mahdollista seuloa erinomaisella tarkkuudella [Receiver operating characteristic (ROC) -käyrän alle jäävä pinta-ala 0.99] ja keliakia hyvällä tarkkuudella (tytöt 0.88 ja pojat 0.84), kun kasvua seulotaan usealla kasvuseulasäännöllä yhtä aikaa.

Sähköistä potilastietojärjestelmää on hyödynnetty vain vähän perusterveydenhuollon diagnostisena apuvälineenä. Väitöskirjan viidennessä osatyössä tutkittiin kasvun tietokoneavusteista seurantaa, mikä paransi selvästi kasvun seulonnan tarkkuutta perusterveydenhuollossa. Kasvuun vaikuttavat sairaudet oli mahdollista tunnistaa noin kuusi kertaa paremmin, ja usein selvästi aiemmin, kun verrattiin automatisoitua kasvun seurantajärjestelmää perinteiseen käsin tapahtuvaan laskentaan perustuvaan menetelmään.

Uudet menetelmät lasten kasvun seurantaan terveydenhuollossa ovat nyt käytettävissä. Tutkimusnäyttöön perustuvat automatisoidut kasvun seurantamenetelmät parantavat seulonnan osuvuutta ja voivat aikaistaa kasvusairauksien tunnistamista perusterveydenhuollossa.

Luokitus: WS 103, WS 104, WS 141, WB 286, WX 175, QS 677, WD 175
Yleinen Suomalainen asiasanasto: kasvu; lapset; keliakia; kasvukäyrät; painoindeksi; pituuskasvu; seulonta; seuranta; tietokoneavusteisuus; Turnerin oireyhtymä

Acknowledgements

This study was carried out in Department of Pediatrics, Institute of Clinical Medicine, School of Medicine, Faculty of Health Sciences, and University of Eastern Finland during the years 2009 to 2014.

I wish to express my sincere gratitude to my first supervisor Professor Leo Dunkel, M.D., Ph.D for his enormous support for my work. Leo had launched the up-dating process of Finnish growth references years before I was privileged to join his research group in 2008. His expertise has guided me throughout these years. Leo, it has been a great honour to be your apprentice in this field of science!

I am immensely grateful to my second supervisor Docent Ulla Sankilampi, M.D., Ph.D. for her inspiring co-operation and encouragement on my thesis. She has always supported me with her admirable innovativeness. Ulla's boundless enthusiasm for science always brings out the best in everyone. Ultimately, she has also become a very good friend.

I wish to thank the official reviewers of this thesis, Professor Harri Niinikoski, M.D., Ph.D. and Docent Risto Lapatto, M.D., Ph.D. for their prompt communications and constructive comments.

I am deeply grateful to Pétur Júlíusson, M.D., Ph.D. for accepting the invitation of being the opponent for the public examination of my doctoral dissertation.

I wish to express my sincere gratitude to Professor Raimo Voutilainen, M.D., Ph.D. for accepting the request of being the custos of the public examination. I'm also grateful for your guidance and expertise in pediatrics.

I want to express my thanks to my closest co-workers Marjo Karvonen, M.D. for her kind support and friendship, and Marja-Leena Hannila, M.Sc her for statistical advice. I also wish to express my gratitude to Eeva Heikkilä, R.N. and Anneli Paloranta, R.N. for their help in data collection.

I also wish to thank my co-workers for their contributions to this thesis: Docent Outi Mäkitie, M.D. Ph.D., Docent Marja-Terttu Saha, M.D., Ph.D., Docent Päivi Miettinen, M.D., Ph.D., Docent Tiina Laine, M.D., Ph.D., Vesa Kiviniemi, Ph.L., Samuli Harju, B.M. and Kari Kesseli, M.D. I also thank Ewen MacDonald, D.Pharm. for the linguistic revision of the thesis. I am also thankful for Karoliina Määttä, M.D., Terhi Nuutinen, M.D. and Laura Valpio, M.D for their generous help.

I express my warm thanks to colleagues in my research group Tanja Kuiri-Hänninen, M.D., Niina Hyvönen, M.D., Panu Kiviranta, M.D., Ph.D. and Sanna Silvennoinen, M.D. for their encouragement during these years. I am also grateful to Ismo Makkonen, M.D., Ph.D., Marja Ruotsalainen, M.D., Ph.D., Katri Backman, M.D., Aino Mäntyselkä, M.D. and Kaisa Vepsäläinen, M.D. for their support, and particularly, for enjoyable discussions during lunch time.

I warmly thank all my colleagues in the Department of Pediatrics, Kuopio University Hospital. Especially, I want to express my sincere thanks to Hanna Huopio, M.D., Ph.D. and Professor Jarmo Jääskeläinen, M.D., Ph.D. for their helpful attitude in solving my (many) clinical challenges in pediatric endocrinology.

"Dinosaur of pediatrics" wishes to express sincere gratitude to Brotherhood Pasanen for enjoyable moments spent together.

I wish to thank my parents-in-law, Soili and Jari Hämäläinen for the sincere help and support that our family has received. I also thank my sister-in-law Annu Suvinen and brother-in-law Antti Suvinen for their enjoyable friendship.

My sincere thanks go to all my friends and their families. Especially, I wish to thank my childhood friends Matti Jokinen, Olli Paavola and Mikko Manninen; we were the "Little boys" who were not allowed to get in the "Big boys'"car. However, I'm also grateful to the "Big boys" Mikko Jokinen, Juha Nivala and Marko Pehkonen for the good companionship.

I want to express my deepest gratitude to my parents Kristina and Tapani for all that loving care and encouragement that you have provided in my life. Your generous support for me and my family has been indispensable. I am also thankful to my older brothers Petri, Samppa and Mika and their families. Your common sense has brought me repeatedly back to solid ground.

I am very grateful to my dear children Helmi, Niilo, Okko and Olavi. You are my "meaning of life"! Pampula, I am always totally amazed by your artistic talent. Nikke, your sense of humor is marvelous. Oki, it is incredible that your glass is always half-full. Olli, you are gifted with great wisdom and sensitiveness.

Finally, my dearest thanks go to beautiful, loving wife Henna, whose encouragement and support have carried me through this project. Walking to the altar with you has been the best thing in my life. You have been my tireless guide in this endless orienteering from check point to check point. I love you!

Siilinjärvi, February 2015

This study was financially supported by Kuopio University Hospital, The National Graduate School of Clinical Investigation and The Finnish Funding Agency for Innovation.

List of the original publications

This dissertation is based on the following original publications, which are referred to in the text by Roman numerals I-V:

I Saari A, Sankilampi U, Hannila ML, Kiviniemi V, Kesseli K, Dunkel L. New Finnish growth references for children and adolescents aged 0 to 20 years: Length/height-for-age, weight-for-length/height, and body mass index-for-age. *Ann Med*. 43: 235-48, 2011.

II Saari A, Sankilampi U, Dunkel L. Multiethnic WHO growth charts may not be optimal in the screening of disorders affecting height: Turner syndrome as a model. *JAMA Pediatr.* 167: 194-5, 2013

III Saari A, Sankilampi U, Hannila ML, Saha MT, Mäkitie O, Dunkel L. Screening of Turner syndrome with novel auxological criteria facilitates early diagnosis. *J Clin Endocrinol Metab*. 97: E2125-32, 2012

IV Saari A, Harju S, Mäkitie O, Saha MT, Dunkel L, Sankilampi U. Early detection of celiac disease using growth in height and weight in screening. *Accepted for publication in JAMA Pediatr. 2015.*

V Sankilampi U, Saari A, Laine T, Miettinen PJ, Dunkel L. Use of electronic health records for automated screening of growth disorders in primary care. *JAMA*. 310: 1071-2, 2013

Contents

Abbreviations

AGA	Appropriate for gestational age
AH	Adult height
AIC	Akaike information criteria
AM	Automated growth monitoring strategy
AUC	Area under curve
BCPE	Box-Cox Power Exponential
BIC	Bayes information criteria
BMI	Body mass index
CD	Celiac disease
EHR	Electronic health records
EMA	Endomysium antibodies
GAIC	Generalized akaike information criteria
GAMLSS	Generalized Additive Models for Location, Scale and Shape
GH	Growth hormone
GHD	Growth hormone deficiency
HSDS	Height-for-age standard deviation score
ICP	Infancy-childhood-puberty
IgA	Immunoglobulin A
IGF-1	Insulin like growth factor 1
IOTF	International Obesity Task Force
ISS	Idiopathic short stature
LGA	Large for gestational age
MPH	Mid-parental height
OCP	Optimal cut-off point
ROC	Receiver operating characteristics
SGA	Small for gestational age
SD	Standard deviation
SDS	Standard deviation score

SM	Standard growth monitoring strategy
TH	Target height
TS	Turner syndrome
tTG	Transglutaminase titer
UK	United Kingdom
WHO	World Health Organization

1 Introduction

Assessment of growth is a fundamental component in preventive child health care. Growth monitoring is intended to detect childhood illnesses, ideally before any other signs or symptoms of the disease have appeared. Several important tools are used in this screening process e.g. growth reference curves depicting "normal growth" in the population, cut-off values defining abnormal growth, preferably as part of a systematic growth monitoring program (1).

The Finnish growth reference values were based on auxological data of children born between the years 1956 and 1973 (2-4). However, contemporary children have had an ongoing tendency to grow taller than their parents (5-8), a phenomenon called "a positive secular change", arising from changes in environmental factors which previously prevented full expression of the individual growth potential (9). Due to these secular trends in growth, the growth references need to be updated periodically (5). However, the magnitude of the positive secular change in height has decreased in Northern Europe in recent years (10), but studies from Finland are lacking.

Due to the paramount importance of genetic factors in the regulation of growth and adult height (AH) (11-14), it is imperative that growth references are based on a population with the same ethnic and genetic backgrounds as present in the intended population (15-19). In 2006, the World Health Organization (WHO) published multiethnic growth charts based on growth data of breastfed children younger than 5 years (20). Nevertheless, the basic idea inherent in the WHO's growth references was the assumption that there was a similar growth pattern under optimal conditions in all humans irrespective of genetic background, a hypothesis criticized by several researchers (15,18,21,22). In these studies, the proportions of healthy children outside the ±2SDS of WHO references were different than expected. In addition, the feasibility of using multi-ethnic growth references for screening of growth disorders has never been tested.

Body mass index (BMI) (weight/height^2, kg/m^2) is considered as the best tool for monitoring the adiposity in both children and adults because of its independence on height, its correlation to body fat, and its ability to predict mortality (23-25). In contrast to the situation in most countries, BMI has not been used in adiposity assessment in children in Finland; instead, the percentage of the median weight-for-height has been used (2-4). Thus, there is a need for a Finnish BMI reference to monitor weight in children and adolescents.

There is a wide variation in growth monitoring programs worldwide, and a substantial amount of health resources are allocated for childhood growth assessment (1,26,27). Despite the widespread traditions of growth monitoring, population-based cut-off values defining normal and abnormal growth are virtually absent (1), and there is little information on how these parameters should be used in clinical practice (1,26,28-30). The adoption of electronic health records (EHR) presents an alternative to develop automated growth monitoring programs (31,32), but these alternatives have not been evaluated systematically.

The primary aim of this study was to investigate and develop modern methods for use in growth monitoring program for children, starting from the assessment of growth and moving towards a well-established clinical practice to detect accurately abnormal growth in primary care. Thus, initially, up-to-date growth references were constructed for Finnish children and adjusted for secular trends in growth. Secondly, the new national growth curves were evaluated against multi-ethnic growth curves. Thirdly, cut-off values for

abnormal growth were established and validated in two target conditions: Turner syndrome (TS) and celiac disease (CD). Finally, the effectiveness of the novel computerized and automated growth monitoring program, in which screening algorithms were integrated into an EHR system, was compared to the manually operational approach in primary care.

2 Review of the literature

2.1 HISTORICAL ASPECTS OF GROWTH MONITORING

For more than a century, growth monitoring has been widely accepted as being an important component of preventive health care in children (33). Originally, the interest for assessing childhood growth was based on the concept that growth reflected general health and well-being as "a kind of mirror for health" (34). The divergence between normal and abnormal growth was already noted by the pioneers of auxology (34). Thus, the need for growth references that reflected normal growth was established already in the late nineteenth century, after these seminal observations of healthy and unhealthy growth in children.

The history of growth studies begins with a description of the human growth written by the Greek poet Solon the Athenian in the sixth century BCE. He divided the human life into ten seven year periods, "hebdomas", of which the first three described surprisingly accurately growth from infancy to adulthood. Nevertheless, the actual studies into human growth started in the eighteenth century, when the interest in human height came from the military who wished to recruit the tallest men who were considered to be strongest in battle. Christian Friedrich Jampbert was the first to publish the aggregated measurements of human growth in 1754 (35). Twenty years after Jambert's thesis, the famous growth description by Philbert Guéneau de Montbeillard including the measurements of his son was published by the family friend, George-Louis Leclerc Buffon, in his fourth supplementary volume of Natural History in 1777 (36). Montbeillard's son had been measured at approximately semiannual intervals from birth to 18 years of age and this description provided excellent longitudinal data on the growth of an individual child. Buffon noticed the seasonal effects on the growth of this individual child, with a higher growth velocity during summer months. Even though Buffon analyzed intensively the Montbeillerd's son's growth, he did not apparently plot the height measurements against age as Richard Scammon (height against age) (37), and D'Arcy Thompson (height velocity against age) (38), did in their famous figures published in 1927 (Figure 1A) and 1942 (Figure 1B).

The next step in growth studies took place in the late eighteenth and early nineteenth centuries with large population-based datasets collected from army recruits in Europe. The earliest descriptions on secular trends in growth were made already in those years, including observation of the generally taller conscript from one generation to the next. An explanation for this phenomenon was not presented before the twentieth century. Apparently, the main purpose for these databases was to provide suitable equipment and clothes for the conscripts. At the same time, however, Carl Eugen used the longitudinal data of over 2,000 pupils of Carlschule School in Germany in 1770's to argue that height velocity would reflect the individual health status better than attained height (33). This hypothesis was presented over one hundred years before the modern methods for growth monitoring had been devised.

A large scale interest for height measurements increased in the nineteenth century, resulting in the fundamental finding that height was normally distributed. Adolphe Quetelet was one of the researchers with the observation of the "Gaussian errors around the mean" (39), thereafter called standard deviation (SD). In those times in the nineteenth century, the epidemiologists pointed out the association between hard work and poor

growth in children. These observations resulted in the proposal made by Charles Roberts as early as 1876 that too short and thin children should not work in factories (40).

Francis Galton presented percentiles around the mean height in the late nineteenth century (41), and these curves were further developed by Henry Bowditch in the United States (42). He had then the revolutionary concept that "growth is guide to health" (43). Franz Boas established the charts with given SD scores (44), but it was not until 1922 that T. Brailsford Robertson constructed the novel method for growth monitoring, the first growth charts with mean height and ±1 and ±2SD curves plotted against age (45).

At the same time with the development of height monitoring methods, the early auxologists had noted the dependence between weight and height in children. Dumoutet was one of the first to publish harmonious weight tables with corresponding heights in 1921 (46). After the first publications, weight-for-height became a widely accepted method to be used in weight assessment. However, the early auxologists observed that the weight-for-height charts failed to account for the actual age of the child. Quetelet had devised and published an index for body composition as early as 1871, the body mass (kg) divided by the square of height (m2), better known as BMI (kg/m2) (47). Thus, BMI is also called Quatelet's index. Nonetheless, it took until the end of the twentieth century before BMI-for-age became established in the growth monitoring of children.

In Finland, the first auxological studies were conducted at the turn of nineteenth and twentieth century. They followed the contemporary European example and gathered large sets of anthropological data from schools and conscripts from different parts of Finland (48). Fredrik Westerlund's auxological database which included growth data of 131,697 men from the military registers was one of these early Finnish growth surveys (49).

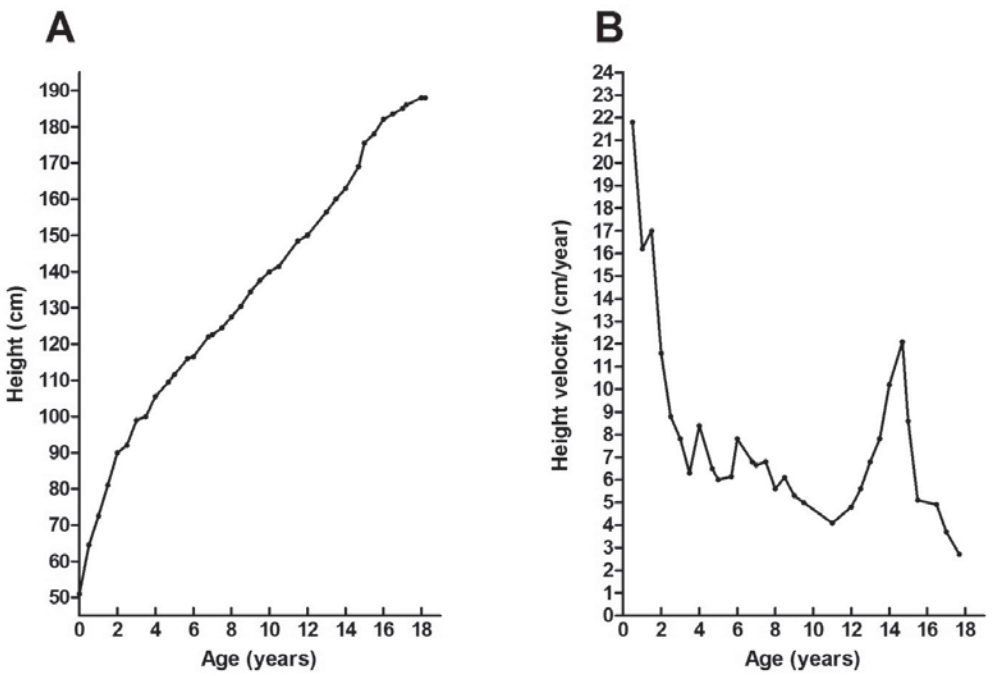

Figure 1. Height-for-age (A) and height velocity-for-age (B) of Montbeillard's son. Modified from A History of the Study of Human Growth (33).

He observed an association between AH and the mother tongue, but also regional differences in the AH. Mean AH in men was 168 cm, being the highest in Swedish-speaking men and in the Western part of Finland. In 1916, Finnish school teacher Ivar Wilskman performed growth studies among children aged 7 – 20 years (50); these are the oldest Finnish publications with serial height and weight measurements. He had continued Fredrik Westerlund's intensive work in assessing regional and social differences in the heights of Finnish children. He also observed the positive secular trend when comparing his data with the earlier Finnish studies. In 1926, Hjalmar Söderström's published the first Finnish growth charts entitled "harmonized weights" for Finnish children (51). These charts were based on measurements of over 5,800 pupils in the city of Helsinki. However, the first proper Finnish growth curves were published as a part of the doctoral thesis of Leena Bäckström-Järvinen only as late as 1964 (48). She conducted cross-sectional and semi-longitudinal studies in different parts of Finland, and compared these with each other as well as with findings from other countries. As an appendix of her thesis, the height-for-age and weight-for-age curves for Finnish children were published. Nonetheless, growth curves were not implemented into the Finnish healthcare system before 1970's (2), in spite of Arvo Ylppö's remarkable pioneering work at well-baby clinics throughout the twentieth century. Eventually, increasing interest in growth monitoring in Finland was triggered after the publications of updated growth reference values by Ritva Sorva in 1984 (2). Her research group's work for cut-offs for screening of abnormal growth (3,4), was the first attempt anywhere in the world to develop an evidence-based growth monitoring program at the population level and remains exceptional even today (1,30).

This brief history of growth monitoring was mainly based on the excellent overview on the evolution of study of human growth written by the late James M. Tanner (33). Tanner's significance as one of the most important individuals in modern auxology is emphasized by his numerous publications on pediatric endocrinology, as well as his uncompromising work in the development of growth monitoring tools and thus for healthier children.

2.2 HUMAN GROWTH

Human growth is a complex process which is mainly genetically but also environmentally determined. The increase in body size due to the proliferation of tissues is regulated by several hormonal and environmental factors. Most of the growth in height occurs in the growth plates located between epiphyses and metaphyses of the long bones.

2.2.1 Phases of growth

Normal linear growth from conception to adulthood consists of four main phases: fetal, infancy, childhood and pubertal (ICP) growth (Figure 2) (52-55). In reality, human growth is continuum of these periods that have specific regulators and controlling factors, and the attained height is considered as the sum of these phases.

Fetal growth is dependent on maternal health and nutrition and linked with placental function. Birth size is genetically determined and its heritability is estimated at approximately 50% (56,57). The growth of the fetus is the most rapid in the second trimester when the growth rate can be as high as 2.5 cm per week (58). Fetal growth in favorable circumstances is regulated by fetal internal growth factors, however, the linear growth is very vulnerable to environmental factors present during this period. Any disturbances in fetal growth may not be corrected later in life. In the third trimester, uterine and placental factors tend to restrict the fetal growth, and the growth of fetus decelerates at the end of the normal pregnancy.

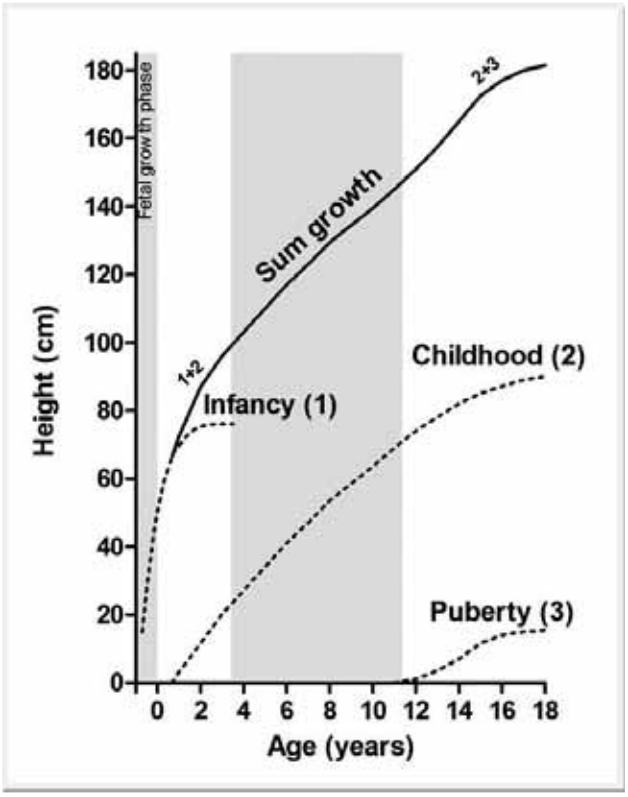

Figure 2. Infancy-childhood-puberty (ICP) growth model. Average growth patterns of Finnish male during infancy (1), childhood (2), puberty (3), and sum growth (1+2 & 2+3) are shown. Derived from Karlberg et al (52-55).

Fetal growth failure may originate from congenital syndromes, chromosomal abnormalities or growth disorders (see Table 1, page 10). Alternatively, impaired growth may be attributable to placental factors, such as abnormal implantation and vascularization of placenta, or maternal reasons including malnutrition, hypertension, toxemia, gestational diabetes mellitus, medication or cigarette smoking during pregnancy. However, the etiology of intrauterine growth retardation cannot be often resolved.

At birth, newborn infants are classified as small, appropriate, or large for gestational age (SGA, AGA, or LGA) according to their birth size. In general, the infant's size at birth is an indicator of prenatal well-being, and thus its evaluation also provides a simple tool for estimating the risk of abnormal perinatal and long-term outcomes.

After birth, the velocity of infant growth is rapid but also rapidly decelerating during the first year of life, so that it is approximately 25 cm/year (Figure 3A). The growth rate declines most markedly during the first 6 months of life, and thereafter this is followed by an average growth velocity of 10 to 15 cm/year until 2 years of age. Nutritional factors are important regulators of growth during infancy, but also hormonal regulation, e.g. mediated by growth hormone (GH) – insulin like growth factor 1 (IGF-1) -axis, thyroxine, sex steroids and glucocorticoids also have recognized key roles for infant growth.

Weight is averagely gained rapidly after birth, reaching a maximum velocity of 13 kg/year for boys and 11 kg/year for girls at the age of one month (Figure 3B). After the peak weight velocity, the gain in weight occurs more slowly until 8 months of age. In children from 1 to 2 years of age, the average weight gain velocity is approximately 2 to 3 kg/year.

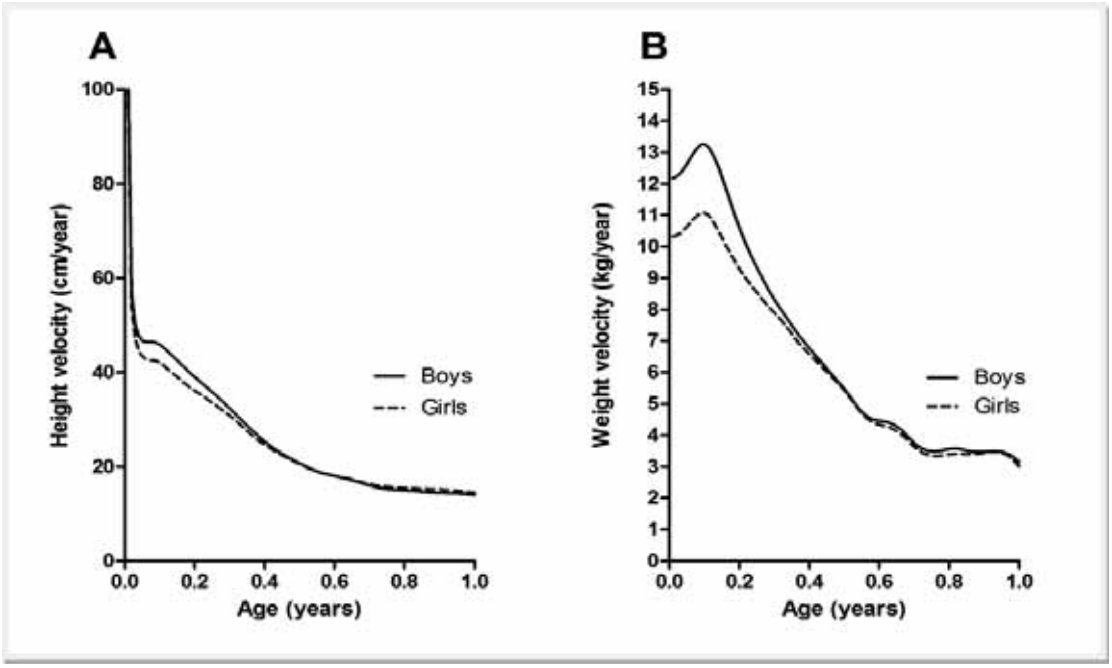

Figure 3. Mean height (A) and weight (B) velocity in Finnish boys (solid lines) and girls (dashed lines) from birth to 2 years of age (I).

Catch-up or catch-down growth, particularly in SGA and LGA children, is a characteristic of infant growth. During this period, growth is normally trajectorized into its own channel. For example, conditions that have transiently suppressed fetal growth (SGA) are assumed to accelerate growth rate (catch-up growth) after inhibiting factors are removed. Conversely, a condition that has led to LGA will often result in catch-down growth during infancy. The underlying mechanism behind this phenomenon is not clear, but recent experimental and clinical findings have found evidence for direct regulatory elements in growth plates with limited replicative capacity of chondrocytes (59,60), also called "growth plate senescence".

The second phase of postnatal growth according to the ICP-model, the childhood growth phase, begins from 6 to 9 months of age as an infancy-childhood growth spurt (61) that is a short acceleration of growth velocity during infancy, and a delay in this spurt is associated with short adult stature (62). The childhood growth predominates from 2 to 3 years of age, and continues until the onset of the pubertal growth spurt. Nutrition becomes less important in the regulation of growth during childhood. Instead, the GH – IGF-1 -axis plays a key role in launching the infancy-childhood growth spurt (63,64). Growth impairment in many growth disorders during childhood is known to originate at least partially from a dysfunction of the GH-IGF-I axis. Nonetheless, GH has an important impact in childhood growth and thyroid hormone is also necessary for normal skeletal growth and maturation. It has dual role in bone growth. Longitudinal growth is promoted by direct action on the growth plate (65), and indirectly by regulation of the GH-IGF-I axis (66,67).

During mid-childhood, growth may be accelerated due to the activation of the adrenal cortex and increased secretion of androgenic hormones, a phenomenon called adrenarche (68). Some of these children show signs of androgenic action including the presence of pubic hair, oily skin and adult-type sweating and body odor (69).

The third phase of the ICP-model, the pubertal growth phase occurs on average 2 years earlier in girls than in boys Characteristically, children undergo a short growth velocity deceleration before the onset of pubertal growth spurt that occurs on average 10 years of

age in girls and 12 years of age in boys (70). The mean age at peak height velocity is 12 years in girls, and 14 years in boys, respectively (70). However, there has been a secular trend for earlier timing of pubertal growth phase in recent decades (70). On average, boys are only slightly taller than girls before puberty, and the majority of the difference in AH is a result of the later and more powerful pubertal growth spurt occurring in boys. The regulation of onset and the sustenance of pubertal growth require synergism between the GH-IGF-I -axis and sex steroids (71). The elevated production of estrogen (in girls) and androgen (in boys) accelerates growth, but also stimulates secretion of GH and IGF-I, which are essential for the development the effects of the sex steroids on the growth plate. Both, estrogens and androgens have key roles in the maturation of the growth plates, and eventually, estrogens will terminate the growth via fusion of the growth plates (72,73).

2.2.2 Secular trends in growth

Over the past decades, growth surveys conducted in both the developed and developing countries have reported increases in the AH and earlier sexual maturation, a phenomenon termed a "positive secular change"(5). It is generally assumed that the positive secular change arises from environmental changes i.e. the lessening of those factors inhibiting full expression of the growth potential, e.g. inadequate nutrition and morbidity (9). The increase in the AH mirrors changes in the political and economic environment, and interestingly, a strong association exists between gross domestic product and secular change in growth (74).

Since World War II, the greatest positive secular trend in mean adult height has been observed in Japan, 2.7 cm/decade (75), and smallest in Sweden and Norway, approximately 0.3 cm/decade from 1950 to 1980 (76). The attained increase in mean adult height has determined to be achieved already during infancy and early childhood (5). However, the positive secular trend in height has not compressed height variations considered to be evidence of equal utilization of growth potential within populations in optimal living conditions.

An earlier timing of pubertal growth spurt has been reported among Danish girls and boys (70). This phenomenon was associated with a higher weight before the onset of puberty (77); however, there was a downward trend in the age at which puberty was attained in both girls and boys, regardless of the BMI, suggesting that obesity is not solely responsible for this trend. In conjunction with the secular trends in pubertal growth, age at menarche has declined on average by nearly 2 years from 1920 to 1970 (78).

The tendency towards taller children raises the question: are there any limits to this positive secular trend? Studies conducted among the Dutch who have been the tallest people in the world have shown a halt in the secular trend in the AH (79). The Dutch population is no longer growing any taller (79). The same finding has been also reported in Northern Europe (10). The general belief is that the secular increase in height continues until the genetic potential of the population is achieved. However, our current knowledge of the genetics of stature is insufficient to allow us to make any realistic estimation of the height potential of population.

Overall, stature is strongly genetically determined in the general population, with heritability estimated at approximately 80% (80). To date, several genome-wide-association studies on the genes regulating stature have been published, mostly on Caucasian-based populations. These studies have identified more than 50 well replicated loci which are associated with stature (11-14). Because of the polygenic nature of stature, there are notable differences in the average height between populations with different genetic backgrounds (5-8,81). These can be explained by various mixtures of alleles associated either with short or tall stature. For the same polygenic reasons, the variation of height (i.e. SD of height) is similar between populations.

2.2.3 Growth disorders

A child's growth is considered an indicator of his or her general health and well-being, and failure to grow or failure to thrive is an early sign for poor health. Several conditions and illnesses could decelerate or accelerate linear growth. In addition, some growth disorders are typical for certain growth phases. An understanding of the regulatory factors involved in the different growth phases provides an opportunity to focus in appropriate clinical investigations of impaired growth. For example, wasting during infancy could be caused more likely from malnutrition, whereas failure to grow during childhood would be more likely to be attributable to growth hormone deficiency.

Malnutrition is the main reason for growth failure in the developing countries, whereas congenital or acquired conditions are the most common reasons for growth impairment in the Western countries. Growth disorders causing short or tall stature are classified into primary, secondary, or idiopathic growth disorders (82). Short stature is often the only or the most obvious clinical sign of a growth disorder, such as in TS (28).

There are some other common disorders leading for stunting, for example hypothyroidism, CD, growth hormone deficiency (GHD) and inflammatory bowel diseases. Growth disorders resulting in tall stature, however, are more infrequent than disorders leading to short stature, and include some common growth disorders, such as precocious puberty. The reasons for short or tall stature classified according to the European Society of Paediatric Endocrinology (ESPE) are presented in the Table 1 (82).

TS is a congenital syndrome in girls that affects approximately 1/2,500 live births (83). The karyotype of TS girls shows a missing or partially missing female sex chromosome X. Various phenotypes exist, but the most common features in children, which affect over 90% of recognized patients, are short stature due to GHD or growth hormone resistance, and premature ovarian failure (28,83). Although, TS is a congenital syndrome it can present at almost any age from perinatal period to adulthood. Typically TS is diagnosed in three time windows postnatally (83,84): 1. neonatally by short stature or lymphedema, 2. during adolescence due to a lack of pubertal development, and 3. during adulthood as infertility. A diagnostic delay in girls with TS is common in the pediatric population (83,84). In addition, TS girls have an increased risk for congenital malformations and aortic coarctation, but also an increased mortality (83), and therefore early detection of TS is crucial.

CD is an immune-mediated systemic disorder elicited by gluten and related prolamines, and the clinical pattern of childhood CD has changed from classical triad –failure to thrive, diarrhea and abdominal distention– and now includes a large variety of nonspecific signs and symptoms, including faltering linear growth, short stature or poor weight gain in children (85-89). CD is still underdiagnosed during childhood: based on serological studies, it has a prevalence of nearly 1:100 in Western populations (90), but only 10 to 20% of these patients are identified (85,90-94). Universal serological screening for CD in the child population would be one option to improve its detection rate, but the benefits and cost-effectiveness of such screening remain controversial and it has not been recommended in the international consensus guidelines for the diagnosis of CD (85,93,94).

Table 1. Growth disorders in children. Modified from the ESPE classification for growth disorders (82). Some of the specific disorders are presented.

Primary growth disorder	**Secondary growth disorder**	**Idiopathic growth disorder**
Short stature		
Clinically defined syndromes *Turner syndrome* *Williams syndrome*	Malnutrition	Familial short stature
Small for gestational age with failure of catch-up growth	Disorders in organ systems *Cardiac disorders* *Celiac disease* *Crohn's disease*	Non-familial short stature
	Growth hormone deficiency	
	Other disorders of the growth hormone- IGF axis	
	Other endocrine disorders *Hypothyroidism*	
	Metabolic disorders	
	Psychosocial	
	Iatrogenic	
Tall stature		
Clinically defined syndromes with sex chromosome abnormality including aneuploidy *Klinefelter*	Growth hormone overproduction	Familial tall stature
Dysmorphic syndromes due to metabolic/connective tissue abnormality *Marfan syndrome*	Hyperinsulinism	Non-familial tall stature
Other dysmorphic syndromes with symmetrical overgrowth *Sotos syndrome*	Familial (isolated) glucocorticoid deficiency	
Dysmorphic syndromes with partial/asymmetrical overgrowth	Hyperthyroidism	
	Conditions leading to tall stature in childhood, and normal or short stature in adulthood *Precocious puberty*	
	Conditions leading to normal height in childhood, and tall stature in adulthood	

2.3 GROWTH MONITORING

Growth monitoring is a cheap and straight forward method to evaluate general health and well-being at the both individual and population level. In developed countries, it is intended to detect childhood illnesses, ideally before any other signs or symptoms of the disease have appeared (1,29,30). The fundamental components of a productive growth monitoring program are accurate methods and equipment for growth assessment including up-to-date growth references and preferably evidence-based tools for screening of abnormal growth, i.e. cut-off limits for abnormal growth (1,28,29).

2.3.1 Assessment of growth

In order to make a reliable assessment of growth is one needs to have standardized equipment and techniques so that the measurement can be reproduced at different times or places and by different people (95). Nevertheless, aims and circumstances of growth assessment vary between developing and developed countries from the itinerant nurses to the buildings of well-baby clinics, thus measuring tools have to be adjusted for the measuring environment. As a part of Multicenter Growth Reference Study conducted by WHO and completed in 2006 (20), extensive recommendations for measuring techniques and recordings were published (95), mainly for healthcare workers in the developing countries. In Finland, comparable recommendations have been issued by the National Institute of Health and Welfare (96). According to the WHO manual, children are weighed with the scales that can be tared for infants with the mothers on it instead of separate baby scales as are recommended in Finland. However, heights are measured identically in both recommendations with a length board in children less than 2 years of age, and a standing board for older children, respectively. The measuring equipment should be calibrated regularly (95).

At each scheduled visit, length or height and weight are assessed using recommended standardized techniques and calibrated equipment. In infants up to age 20 to 24 months, the weight is measured without clothing on calibrated baby scales, and rounded to the nearest 0.005 kg. Length in the lying position or standing height is measured to the nearest 0.1 cm, and standing weight is measured on calibrated step scales and rounded to nearest 0.1 kg. The quality of growth data gathered at routine visits has been assessed in Finland, and it was reported that false measurements, typing errors, missing values, or duplicate recordings are rare (97).

In Finland, approximately one million measurements are performed on children every year. Since the turn of the century, almost all measurements had been captured in the electronic patient management systems with specific programs for growth monitoring that have replaced the manual patient records. Growth data are gathered into EHR, in which longitudinal height, weight and head circumference data can be plotted on which are displayed on the computer screen growth curves. Additional data, e.g. birth size, gestational age, pubertal stage and parental heights, are also included in the EHRs.

2.3.2 Growth references

The main aim of the use of a growth reference is to answer the question: "Is this child growing normally?" Thus, growth curves should be constructed on the auxological data of the reference population, from which abnormally growing patients have been excluded. It is important to understand the conceptual distinction between 'reference' and ´standard´. The reference is only the descriptive for variation in the population as a whole, while a standard defines the variation that is assumed to be normal and healthy under optimal conditions. However, the distinction between "growth reference" and "growth standard" is often indistinct. Cleaning procedures for initial data are intended to end up with normative (standard) growth as accurately as possible, but healthy and optimal growth might be

difficult to delineate. A more or less intensive cleaning process for reference data might result in distortion of the final data. In fact, this is the case with the weight reference. Healthy weight gain is almost impossible to define. Thus, children with growth disorders are excluded from weight reference population only. There are widely accepted methods for exclusions for height reference population to reflect optimal, healthy linear growth are (6,8,20,81):

1. Children with growth disorder or medication possible affecting growth
2. Premature children with gestational age less than 37 weeks
3. Low or unknown birth weight (under 2500g)
4. Extreme height-for-age (outside ±4SD)
5. Underweight or obese children

The use of growth reference curves is an essential component of the effective growth monitoring. These curves describe the variation of auxological measurements in the child population. Growth references are used for health assessment at both the individual level i.e. for identifying an individual as being in need of special consideration, and to assess individual response to intervention; or at the population level assessing prevalence, evaluating trends, detecting subpopulations at risk, and in monitoring the impact of interventions (20,98).

The variation of growth in the reference population is expressed in growth curves between -2 and +2 SD, or the corresponding curves for 2.3 and 97.7 percentiles (Figure 4), which include observations of approximately 95.4 percent of all persons of the reference population. Traditionally, height growth is displayed against age (height-for-age), and weight as a function of height (weight-for-height or BMI-for-age), due to fact that body mass depends on both lean mass (mostly height growth) and fat mass.

Data collection for growth references may be carried out cross-sectionally, longitudinally or by a mixed-longitudinal design; the method being chosen mainly depends on how the data is to be interpreted (98). Generally, growth curves are based on cross-sectional studies, in which children of different ages are measured once at the same point of time. These growth surveys are relatively easy to perform, and data can be analyzed immediately.

Cross-sectional growth references, however, do not provide accurate information on growth rate and therefore these curves are not suitable for longitudinal growth monitoring. Instead, this kind of data demands a longitudinal design including repeated measurements in the same children. Curves base on longitudinal data can be delineated with a smaller sample size than cross-sectional curves. Longitudinal studies, however, are more laborious to carry out because the same individual has to be measured often and that increases the risk for drop-outs and data is more difficult to manage. Moreover, should the time-range between the start and the end of the data collection be a long time, then the reference may have become already outdated by the time of finishing data collection due to a secular change in the population. The mixed-longitudinal design is a compromise from both cross-sectional and longitudinal studies. Individuals in the reference population are measured more than once, but not across the entire age range, allowing for a combination of the benefits of the both data collection methods. Traditional growth references are distance-type growth curves that could be constructed with a cross-sectional sample. Distance references are used in comparison of attained growth between two populations, comparison of attained growth of the same population at different occasions, and one can detect an individual's impaired growth using a single observation located in the extreme percentiles (98). However, longitudinal patterns of growth cannot be assessed by distance growth curves. If one wishes to study growth velocity, a reference constructed from longitudinal collection of data is needed.

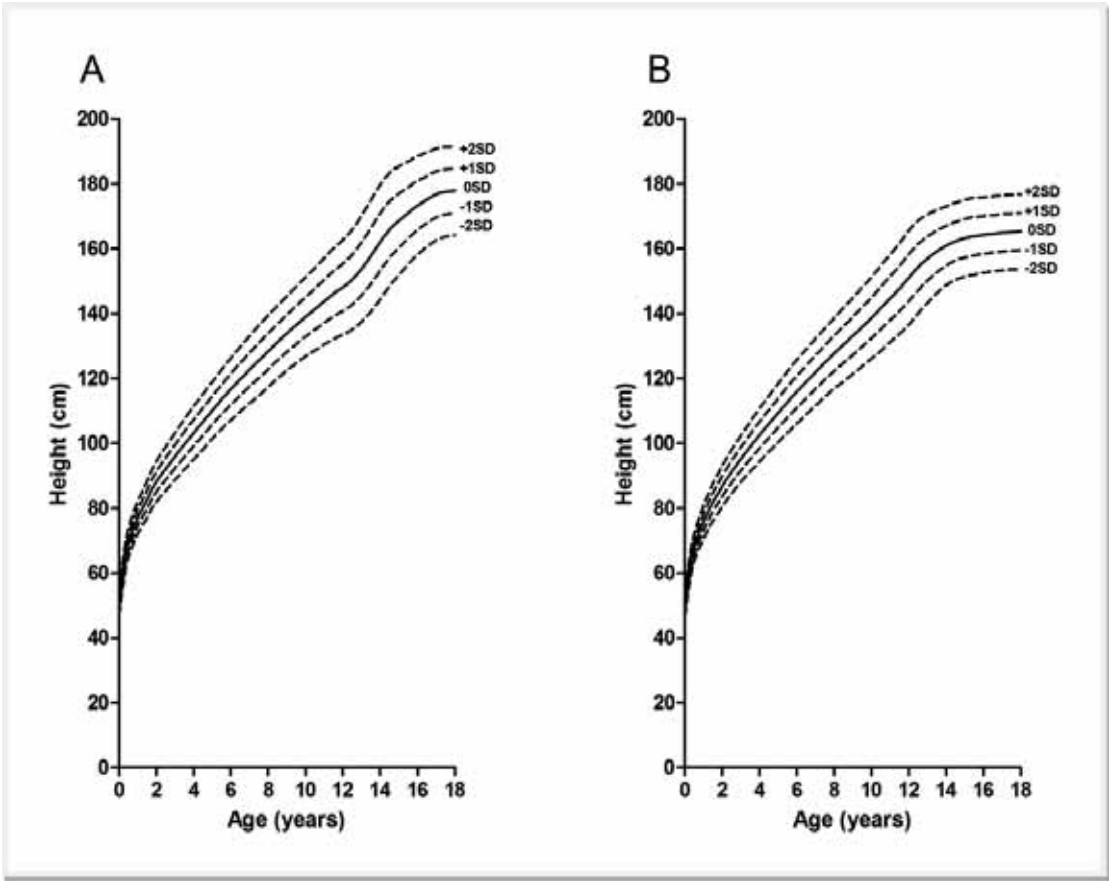

Figure 4. Finnish growth curves for mean height (solid lines) ± 1 & 2 SD (dashed lines) for boys (A) and girls (B) published in 1986 (2-4).

Recent growth studies, for example Dutch (6), Norwegian (8), and WHO Multicentre Growth Reference Study (20), have been invariably based on a mixed longitudinal design. In addition, as a part of the WHO's project the statistical methods were evaluated to determine the best method for curve fitting of data from a mixed-longitudinal setting. This intensive work terminated in an application for the comprehensive method of smoothing for growth curves, known as the LMS-method (L for skewness, M for median and S for coefficient of variation) by Cole and Green (99,100), the Generalized Additive Models for Location, Scale and Shape (GAMLSS) (101), in which it is assumed that age-conditional distribution is normal after applying a Box-Cox type transformation. The major advantage of the method is that after transformation of the data that are originally not distributed normally, these can be managed as if they were normally distributed, and the values for attained growth can be transformed to SD scores (SDS).

Longitudinal growth data collected in a mixed-longitudinal setting can be utilized for generating conditional references. However, the interpretation of the growth rate over time is affected by the regression to mean (102) that is a statistical phenomenon encountered with repeated measurements in a single individual. A child growing in an extreme percentile is expected to be less extreme in the next observation. The conditional reference proposed by Cole (103), takes this kind of regression towards the mean into account.

The Finnish growth references were launched in 1986 and are based on height and weight measurements of 2,305 children born between 1954 and 1972 (2-4). In Finland, height growth is interpreted as SDS against age (2), therefore growth curves for mean

height ±2SD are drawn as horizontal lines (Figure 5). In addition, in contrast to most Western countries, weight is assessed as a percentage of the median weight-for-height, instead of BMI-for-age percentiles (2-4,104). Data correlating BMI and weight-for-length/height in childhood are scarce. A single study from the United States revealed a poor correlation, indicating that these two endpoints are not interchangeable (105).

Growth curves have to be renewed regularly due to secular changes. Theoretically a secular shift up to +0.4 SDS in the average height would result in a 3.4% reduction in specificity and up to a 32.6% reduction in sensitivity in the screening of short and tall stature with cut-off points at ±2 SD.

In 2006, the WHO published multiethnic growth charts for breastfed children younger than 5 years (20). Those WHO curves are intended to show how children grow under optimal conditions irrespective their genetic background. Originally, the rationale for the construction of the multiethnic WHO references stemmed from an earlier study that reported very similar growth patterns in infants and children from diverse ethnic backgrounds when their physiological needs are met and their environment can support their healthy development (106,107). Nevertheless, in recent studies from Norway and Belgium, proportions of the healthy children outside the ±2 SDs of WHO standards were different than expected (15).

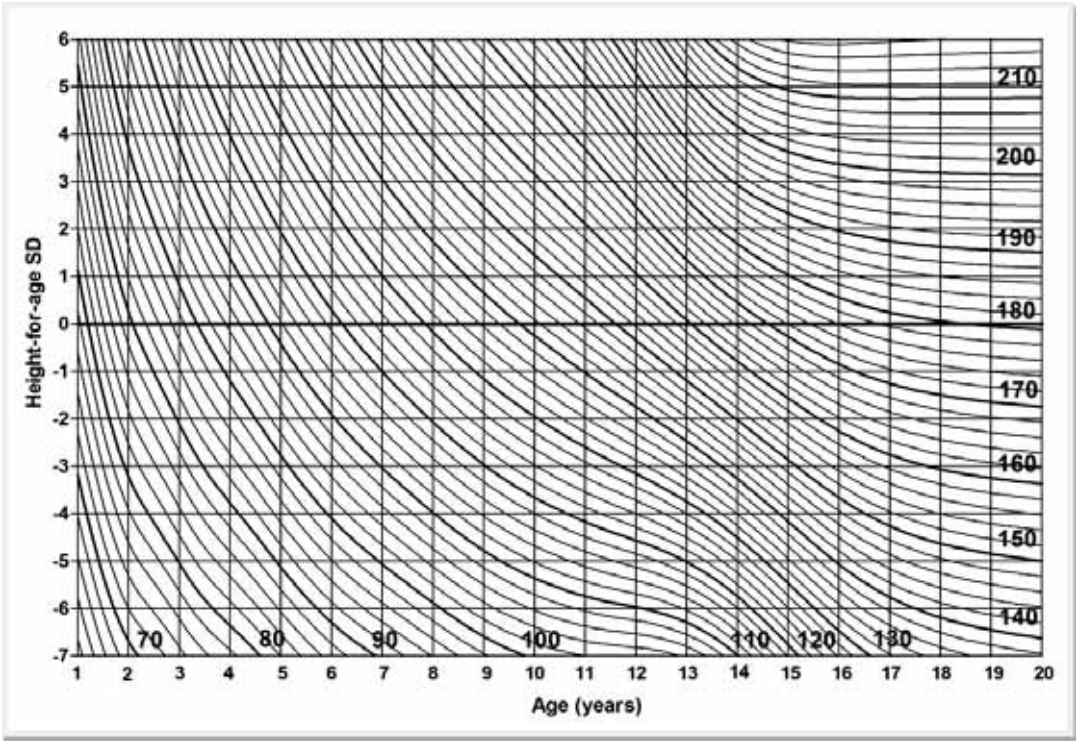

Figure 5. Height-for-age growth reference of Finnish boys aged 1 to 20 years expressed as SD-values. Growth curve is plotted by using height isometers (70 – 210). Derived from Sorva et al (2).

Moreover, children in Hong Kong living under optimal conditions (same inclusion criteria as used by WHO), on average were shorter than the mean of the multi-ethnic growth reference (18). Data collection of WHO growth references has also been criticized due to selective drop-out (108). Thus height assessment in children growing at the outer percentiles with potential morbidity may be flawed if one uses the WHO standards. However, WHO's growth curves are applicable at least in countries without national growth references (20).

In the recent decades, western countries have been alarmed by an epidemic of obesity (109-111). In Finland, the prevalence of overweight adolescents has almost doubled in the past two decades (112,113). Overweight and obesity often persist into adulthood and are recognized as risk factors for chronic diseases such as cardiovascular disease and type 2 diabetes (114-117). BMI (weight/height^2, kg/m^2) is considered the best tool for monitoring the epidemiology of overweight and obesity in both children and adults because of its independence of height, correlation to body fat, and ability to predict mortality (23,24,118-121). The normal body composition changes from infancy to adulthood. Thus, the reference values for BMI are age- and sex-specific. However, detailed knowledge of BMI thresholds related to morbidity in childhood is still lacking (116,121-123). Nonetheless, there are no BMI-for-age growth curves for Finnish children implemented in electronic health records.

2.3.3 Methods for auxological screening of growth disorders

The main aim of growth monitoring is identification of treatable disorders in an apparently normal child. Early diagnosis helps to minimize the impact of the underlying health condition and to optimize final AH. Thus, growth monitoring meets the criteria as a screening program (124,125) that can identify not only one disorder, but several treatable causes of abnormal growth that might have been overlooked or remained undetected in current practice. In undeveloped and developing countries, weight screening with recent WHO multi-ethnic growth references has been reported to be feasible tool for the detection of malnutrition (126-128), and for monitoring children at risk of pre-term death (129,130). In the developed countries, however, the main focus of growth monitoring programs is in the early detection of disorders affecting linear growth.

Growth monitoring is believed to be efficient if growth impairment is the only or the first sign of a growth disorder, and there are no other clinically obvious symptoms that might be present. TS and GHD are prevalent conditions that are responsible for failure to grow, and which might be identified accurately via growth monitoring (30). There are also other disorders that may be detected for example CD, hypothyroidism and precocious puberty.

The efficacy and accuracy of growth monitoring as a screening test are assessed via specificity and sensitivity (Table 2). Specificity is the proportion of children without a growth disorder who test negative, and sensitivity is the proportion of children with a growth disorder who test positive. The calculations of these screening characteristics are based on true negative and false positive rate for specificity, and true positive and false negative rate for sensitivity (see Table 2). The diagnostic accuracy of growth monitoring is always a trade-off between sensitivity and specificity. Growth monitoring cut-offs are intended to detect as many abnormally growing children as possible (high sensitivity) without producing too many unnecessary referrals or further investigations (high specificity). However, three important differences between growth monitoring and other screening programs have been described by Stef van Buuren and Paula von Dommelen (125). First, an intervention attributable to impaired growth is usually initiated when the patient displays other clinical symptoms, whereas the conventional screening program is only dependent on the result of the test. Second, growth monitoring is not only aimed at identifying a single disorder, unlike traditional screening programs. Third, children growth monitoring could be performed with a time dimension, while a population is tested at one moment or via several tests at a given age (125).

Table 2. Screening specificity and sensitivity

Screening disorder	Screening test positive	Screening test negative
Yes	True positive (a)	False negative (b)
No	False positive (c)	True negative (d)

Specificity = d / (c + d)
Sensitivity = a / (a + b)

Growth monitoring is intended to detect childhood illnesses (see Table 1), ideally before any other signs or symptoms of the disease have appeared. Screening specificity for a single measurement is defined by growth references, but the sensitivity of growth monitoring program will still remain unresolved, if it is not validated with target conditions. Conditions which are important to detect early, and which cannot easily be recognized since there are few or even the complete absence of presenting signs justify population-based screening of growth disorders in general (30). The assessment of diagnostic accuracy for these specific disorders is essential in this validation process of growth monitoring programs.

Evidence-based cut-off values for abnormal growth are needed if growth monitoring is to be considered as a reliable screening program (124,125). Several auxological variables can be utilized for screening process (125), but the simplest and most widely used method is fixed percentile or SD cut-off for the growth reference (see Table 3). This inexpensive and easily carried-out method can be reasonably performed in a cross-sectional setting. In addition, screening specificity is pre-designated, as long as growth curves have been adjusted for the secular trend, and are representative for the given population. For example, a cut-off value 0.5th percentile for short stature corresponds to the screening specificity of 99.5%. However, longitudinal growth data of the monitored children cannot be utilized in fixed percentile cut-off values.

Abnormal growth rate by age can be screened by using conditional growth references. The variation of the growth rate over time is based on the fact that the distribution of the change in height or weight SDSs at a fixed age interval is normally distributed. Thus, screening specificity for growth rate is also pre-defined in the percentile or SD cut-off value. However, longitudinal growth assessment is sensitive for measurement errors, and several calculations between two time points might be laborious if they need to be done manually.

Height varies within a given population, mostly due to familial (which are also mostly genetic) factors. These can be taken into account by using an auxological variable called the target height (TH). TH represents an interesting approach for growth monitoring since it is believed to improve accuracy of growth monitoring, because the height variation in TH is narrower than the variation in height itself (131). Nevertheless, screening with TH method is dependent on both parental heights. Several methods have been proposed for calculating TH (132-134), but their accuracy in the context of growth monitoring has never been tested.

The most widely used adult cut-off values for weight are a BMI value of 25 kg/m^2 for overweight and 30 kg/m^2 for obesity, these values have also been related to increased health risks (110). An International Obesity Task Force (IOTF) expert panel proposed that BMI-for-age percentile curves passing through adult values of 25 kg/m^2 and 30 kg/m^2 could be used for defining childhood overweight and obesity, respectively (110,135). Multi-national curves were subsequently constructed by Cole et al. with grades of 3, 2, and 1 thinness in children defined as BMI-for-age percentiles passing through adult values of 16, 17, and 18.5 kg/m^2 (136), respectively.

2.3.4 Growth monitoring programs

Growth monitoring practices have been adopted worldwide (27), but are hardly ever based on consensus statements or evidence-based screening cut-off values (1,137,138), and therefore the effectiveness of routine growth monitoring is considered as having been insufficiently explored (1,30). There are currently 12 published growth monitoring studies

for height using diagnostic approaches (29,32,139-148). An overview of these publications is presented in Table 3. Most of the studies were based on a single measurement at a certain age (32,139-145,147,148), and 11 of 12 studies utilized simple cut-off values for abnormal growth (percentiles or SDS) that, however, have not been tested in clinical practice. In addition, only three studies estimated the growth rate (29,142,146). Furthermore, longitudinal growth data was not utilized in any of these studies.

The detection rates for growth disorders were reported in nine studies, in which one growth disorder could be detected per 1000 measured children. However, only the one study of Grote et al (29) used evidence-based growth monitoring cut-offs in the evaluation of clinical effectiveness and diagnostic accuracy of a growth monitoring program for their target conditions (TS, GHD, cystic fibrosis and CD). Thus, in the systematic review published by Craig et al it was assessed as the only relevant study that provided a referral strategy for short stature (1). The review concluded that appropriate referral strategies for growth monitoring had still been insufficiently explored.

An effective growth monitoring program should contain the following key components (1,26,30):

1. Measurements are taken with standardized the methods by the trained health care professionals
2. It uses up-to-date and appropriate growth reference (149)
3. Well-established cut-offs for abnormal growth are used
4. It facilitates early detection of disorder(s) affecting growth
5. It results into improved prognosis through earlier detection of disorders

According to the literature search, there are clear differences in the published growth monitoring programs (2-4,29,30). In the UK, a single measurement of less than 0.4th percentile at school entry as a screening program for abnormal growth is used (30). This cut-off value is based on the single study of Voss et al (148), and has never been validated under target conditions. The unused potential of the longitudinal growth data is a clear disadvantage in the UK system.

Finnish primary care represents a unique growth monitoring program (2-4,104). The entire child population is covered by a free-of-charge national health monitoring program, which is enshrined into the law (150). Primary care nurses are trained in child health care and health prevention, and their duties include the assessment of health and development at scheduled visits including standardized weight and height measurements. Finnish children make regular visits to child health clinics at the ages of 1 to 4 weeks; 4 to 6 weeks; at 2, 3, 4, 5, 6, 8, 10, 12, 18, and 24 months, and then at 3, 4, 5, and 6 years of age (96). After six years of age, children and adolescents visit the school health care annually. In addition, children may make extra visits if any distinct health concerns are suspected.

Monitoring strategy includes manual growth evaluation with two screening algorithms, for attained height and growth rate that have been used in Finland since 1989 (Table 4). Screening cut-offs are set to a specificity of 99% corresponding to the 0.5th percentile for short stature, and 99.5th percentile for tall stature, respectively. If the primary care nurse considers the growth to be abnormal, then she/he consults the primary care physician who performs an assessment or baseline investigations and may then refer the child to secondary care.

The Finnish growth monitoring program is extensive. Furthermore, longitudinal growth data is utilized, and screening cut-off values cover also tall stature. However, in clinical practice, these screening rules are considered as too complex and difficult to utilize. Despite the fact that the UK and Finland have long traditions of growth monitoring, the cut-off values have not been validated with evidence-based methods in either country.

Table 3. Overview of the growth monitoring program studies

Study (year)	Monitoring strategy	Monitoring cut-off	Overall detection rate	Target conditions	Screening specificity/ sensitivity
Lacey (1974) (145)	A single measurement of children aged 10	< 3rd percentile, or < -3 SDS	1.77/1000	Any growth disorder	NA
Vimpani (1981) (147)	A single measurement of children aged 6 to 9	≤ -2.5 SDS	0.23/1000	Any growth disorder	NA
Voss (1992) (148)	A single measurement of children aged 5	< 3rd percentile	0.56/1000	Any growth disorder	NA
Cernerud (1994) (142)	A single measurement of children aged 10 and 14	< -2 SDS or > 2 SDS, or > 0.5 SDS change/year	NA	Any growth disorder	NA
Lindsay (1994) (146)	Repeated measurements of children aged 5 and 11 in one year interval	< 3rd percentile, or < -2 SDS, or growth rate < 5 cm/year	0.22/1000	Any growth disorder	NA
Ahmed (1995) (140)	A single measurement of children aged 3 and 4.5	< -2 SDS	0.54/1000	Any growth disorder	NA
Hearn (1995) (144)	A single measurement of children aged 5 and 12	< 3rd percentile	1.15/1000	Any growth disorder	NA
de la Puente (1999) (143)	A single measurement of children aged 5 to 8	≤ 3rd percentile	0.96/1000	Any growth disorder	NA
Keller (2002) (32)	A single measurement of children aged 0 to 19	< 3rd percentile, or > 97th percentile	1.84/1000	Any growth disorder	NA
Banerjee (2003) (141)	A single measurement of children aged 5 to 7	< 0.4thpercentile	NA	Any growth disorder	NA
Agwu (2004) (139)	A single measurement of children aged 4 to 5	< 0.4th percentile	1.15/1000	Any growth disorder	NA
Grote (2008) (29)	Serial measurements of children aged 0 to 10	Flow diagram, (see Figure 6)	NA	TS, GHD, CF, CD	98-98.5%/77-80%

TS = Turner syndrome, GHD = growth hormone deficiency, CF = cystic fibrosis, CD = celiac disease

NA = not available

Table 4. Finnish growth monitoring algorithms for abnormal growth (2-4,104).

I Algorithm	**Cut-offs for height-for-age**
Age < 1 year	Length within 2.3 SD from the population mean
Age ≥ 1 year	Length/height within 2.3 SD from the target height (calculated from parental heights) or within 2.7 SD from the population mean (if target height not known)

II Algorithm	**Cut-offs for growth rate (change in height SDS)**										
	Age (years)										
Preceding time (years)	**0.25**	**0.5**	**0.75**	**1**	**1.25**	**1.5**	**1.75**	**2.0**			
0.25	1.7	1.1	0.9	0.9	0.8	0.7	0.6	0.6			
0.50		2.1	1.6	1.5	1.4	1.3	1.2	1.0			
0.75				2.3	1.9	1.7	1.6	1.5			
	2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
1	1.5	1.4	1.2	0.9	0.9	0.9	0.7	0.6	0.6	0.7	0.7
3			1.8	1.5	1.2	1.1	0.9	0.9	0.9	1.0	1.1
5					1.9	1.7	1.4	1.3	1.3	1.3	1.3

In the Netherlands, screening guidelines for short stature were recently published for Dutch children (29). Details of this programme are presented in Floor Grote's thesis which was published in 2007. In her summary, she proposed guidelines for developing a growth monitoring program organized according to a step-by-step flow diagram for age, attained height and growth rate (Figure 6). Growth screening (referral criteria) cut-off for children more than 3 years of age were very short stature (HSDS < -2.5 SD) or short stature (HSDS < -2 SD) with dimorphic features or small for gestational age. If none the above criteria were not met, however, child should be referred if height SDS deviation from TH was > 2 SD or the growth rate was < -1 SD. For children less than 3 years of age, the referral criteria were extreme short stature < -3 SD or repeated very short stature < -2.5 SD. The clear advantage was that the guidelines for short stature were based on validation studies performed for a few target conditions (TS, GHD, CD and cystic fibrosis) resulting in good sensitivity (varying from 77 to 86%) with acceptable specificity (98 – 98.5%) (29). However, growth syndromes for tall stature were not incorporated into these guidelines.

2.3.5 Computer assisted growth monitoring program

Irrespective of the country, a substantial amount of health resources are invested in childhood growth monitoring. Nonetheless, diseases affecting growth are still diagnosed late with possible detrimental effects on long-term health-related outcomes (1,84,151). Thus, better strategies for childhood growth monitoring are needed.

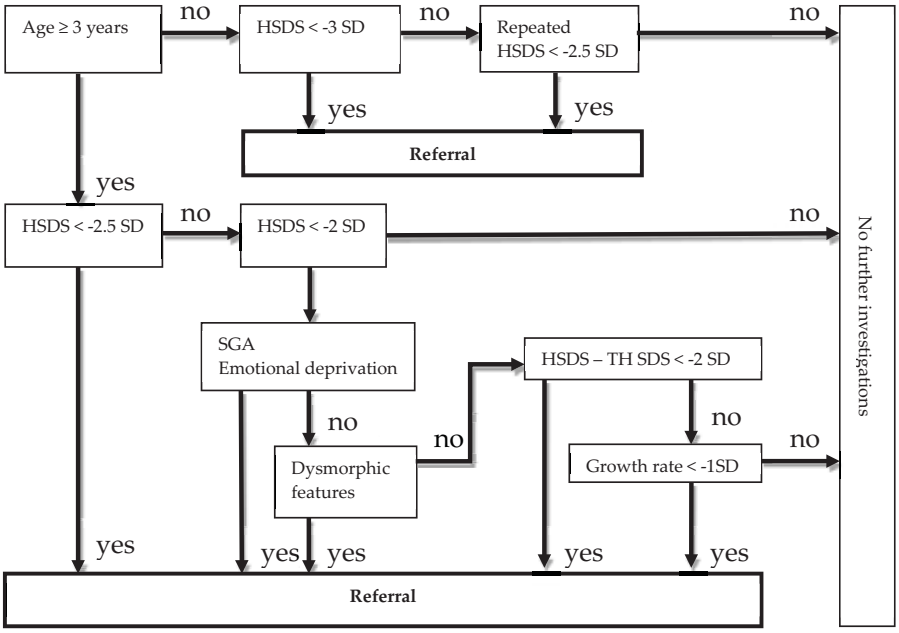

Figure 6. Flow diagram of Dutch criteria for referral of children with short stature. Derived from Grote et al. (29).
Abbrevations: HSDS, Height-for-age standard deviation score; SGA, Small for gestational age; TH SDS, Target height standard deviation score

EHR are widely used in health care throughout Europe (27). Recently published study on growth monitoring practice showed that on average 61% of European paediatricians are utilizing some kind of computer software with which to monitor growth (27). Every fifth was using a simple screening algorithm for abnormal growth, although, those were not implemented into EHR. It is noteworthy that none of the respondents were utilizing any of the published growth monitoring algorithms.

The adoption of EHRs represents an opportunity to develop growth monitoring. Several steps of growth monitoring are suitable for automation, e.g. automated plotting of growth charts, computerized screening algorithms for abnormal growth, and automated flagging of abnormal screening results. In addition, automatic consultation services could be constructed between primary and secondary (or tertiary) care if abnormal growth is detected. It seems that the German program described by Keller et al (32) and Kiess et al (31) is the only computer-based growth monitoring system, in which routine height measurements are gathered on an ongoing basis in more than 100 participating paediatric practices throughout a wide area of Germany. Children with heights above the 97th percentile or below the 3rd percentile on the German synthetic normal curve were highlighted to the relevant practice, and children were referred for specialist investigation if this was deemed necessary. Nevertheless, automated growth monitoring strategies (AM) have not been evaluated systematically. It is not known whether an AM integrated in EHR in primary care will perform better than a standard growth monitoring (SM) strategy based on the primary care providers' interpretation of the child's growth pattern.

3 Aims of the study

The aims of this study were:

- to evaluate secular trends in growth occurring in Finland from 1950s
- to construct new population-based growth references
- to compare the performance of the population-based new growth reference with the multi-ethnic WHO growth reference in detecting abnormal growth, using TS as a model of a growth disorder
- to establish evidence-based screening cut-offs for detection of abnormal growth, and test the performance of these cutoffs using TS and DC as models of growth disorders
- to assess the effectiveness of a computer-assisted growth monitoring program in primary health care.

4 Material and methods

4.1 GROWTH REFERENCES

Data for constructing the new growth references were collected from providers of public primary care in the Southern city of Espoo, Finland's second largest city with a population of 241,600 inhabitants. The majority of the population (94.4%) is of Finnish origin which mirrors the whole of Finland (97.3%). Historically, the population has grown by over 10-fold over the past 50 years with a significant net migration from all parts of Finland (152).

The Finnish social security system provides regular, free-of-charge visits to public primary care child health clinics and school health care to permanent residents of Finland regardless of social status or income level (150). Primary care nurses in Finland are specially trained in child health care and health prevention and their duties include assessment of health and development at these scheduled visits including standardized weight and height measurements. Children in Espoo make regular visits to child health clinics at the ages of 1 to 2 weeks; 3 to 6 weeks; 6 to 8 weeks; at 2, 3, 4, 5, 6, 8, 10, 12, 18, and 24 months, and then at least annually up to 18 years of age. Children may have also extra visits if any special health concerns are suspected.

Length/height and weight are measured using standardized techniques and with calibrated equipment. In infants up to age 20 to 24 months, length is measured to the nearest 0.1 cm in a fully extended supine position with heels in contact with a baseboard. The infants are weighed without clothing on calibrated baby scales, and the weight is rounded to the nearest 0.005 kg. From the age of 24 months, standing height is measured to the nearest 0.1 cm using standardized stadiometers and standing weight is measured with calibrated mechanical or electronic step-scales being rounded to the nearest 0.1 kg. Since 2003, all measurements in the Espoo area had been entered into an EHR (Effica, Tieto Ltd, Finland). The weight and length measured in the birth hospital, as well as data on premature birth have also been recorded in the Effica program at the first visit to the child health clinic.

4.1.1. Data collection, and database cleaning

For the weight-for-length/height and BMI-for-age references, were the auxological data from Espoo recorded in the Effica system between 1 January 2003 and 12 May 2009 used. All potentially false measurements, typing errors, missing values, or duplicate recordings were corrected or excluded. The initial database for weight-for-length/height and BMI-for-age reference contained 561,392 length/height and weight measurements from 75,810 subjects aged 0 to 20 years. Data cleaning occurred in two phases (Figure 7).

First, the primary health care nurses retrospectively evaluated the eligibility of each subject for the new growth reference. These nurses had been specifically trained by a pediatric endocrinologist (L.D.) to exclude medical diagnoses or medications that could have possibly interfered with growth. Second, any potential bias as a result of repeatedly measuring the same subject was eliminated by grouping the measurements into 29 time slots according to the official visiting schedule in the Espoo child health clinics and school health care. Only one measurement per child per time slot was selected (the closest visit to the correct visiting age). The weight-for-length/height and BMI-for-age references were constructed from the resulting mixed cross-sectional and longitudinal database comprised of 73,459 subjects aged 0 to 20 years (35,890 girls and 37,569 boys) with 428,326

length/height and weight measurements. The subjects were born between 9 May 1983 and 5 May 2009.

For the length/height-for-age reference, the initial database was comprised of subjects from the weight reference population who had made at least one scheduled visit between 10 March 2008 and 9 March 2009 (40,655 subjects/285,488 measurements) (Figure 8). The past and present growth data of each measured individual was evaluated systematically by automated screening according to the existing Finnish growth screening rules (see Table 3) (3,4). Children with faltering growth curves identified by the automated screening method were referred to a pediatric endocrinologist who excluded children with suspected abnormal growth curves from the database (see Figure 12). Male data were supplemented by 200 measurements of healthy, consecutive army conscripts aged 18 to 20 years from the Garrison of Santahamina (Helsinki, Finland) and fulfilling the above general inclusion criteria for the database. Military service is compulsory for all healthy young male (aged over 18 years) adults in Finland, and the subjects chosen for the present study originated from the same area of Southern Finland as the whole study population.

Furthermore, subjects (and all their measurements) with conditions possibly affecting growth or significantly differing from the average (i.e., those with prematurity, low or unknown birth weight, height below -4 SD or over +4 SD, and underweight or obesity; (Figure 8) were excluded from the height reference database.

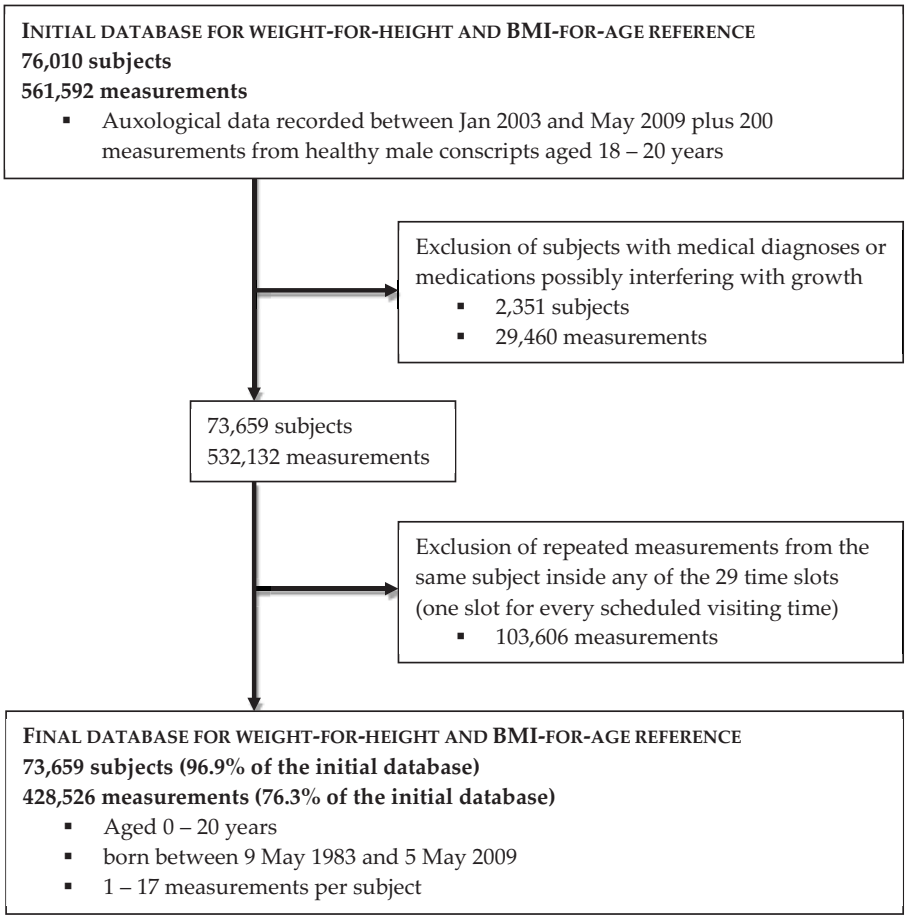

Figure 7. Data cleaning procedure for the weight-for-height and BMI-for-age reference database.

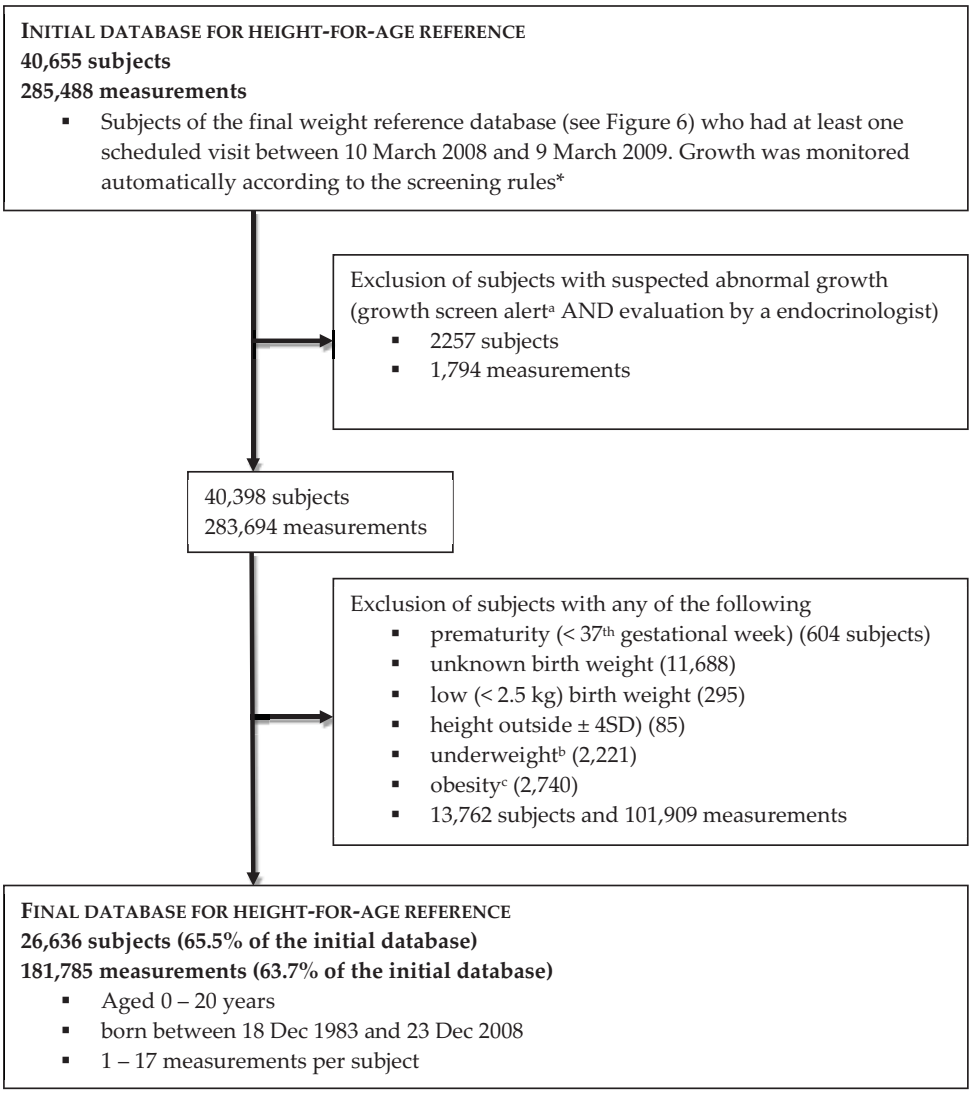

Figure 8. Data cleaning procedure for the height reference database.

[a]Screening cut-off values: height SDS deviation outside ±2.7SD from the mean, or outside ± 2.3 SD from the target height, or change in height SD in the preceding 1, 3, or 5 years exceeding the age-specific cut-off values;
[b]Underweight: weight-for-height below -15 % of the median in height of 50–129 cm, below -20% in height of 130–159 cm and below -25% in height of 160–180 cm;
[c]Obesity: weight-for-height above 20% or 40% of the median weight-for-height in children less than 7 years or 7 years or more, respectively (3,4).

The final database for the length/height-for-age reference included mixed cross-sectional and longitudinal data, including 181,785 length/height and weight measurements of 26,636 full-term, healthy subjects (12,895 girls, 13,741 boys) born between 18 December 1983 and 23 December 2008. The number of measurements per subject varied from 1 to 17.

4.1.2 Curve construction and statistical analysis

In the construction of growth references (length/height-for-age, weight-for-length/height, BMI-for-age), the distribution of response variables and smoothing techniques of the distribution parameter curves over the explanatory variables were chosen by closely following the guidelines provided by the WHO (20). GAMLSS were used, choosing the distribution of a response variable from the flexible Box-Cox Power Exponential (BCPE) distribution family and using cubic splines as a smoothing technique (101). The BCPE distribution can be described in terms of four parameters: M for median, S for coefficient of variation, L for Box-Cox transformation power, and T which is a parameter related to kurtosis.

The R statistical software (GAMLSS package) was used in the analysis (101). First, optimal power transformation was calculated by non-linear regression for the explanatory variable in relation to the response variable as it was found to improve goodness of fit. Second, optimal degrees of freedom for parameter curves were defined using the optimal function and the Akaike Information Criteria (AIC), the Generalized AIC (GAIC), and the Bayes Information Criteria (BIC) (which have penalty h of 2, 3 and log(n) in the formula -2L-hp, where L is the maximized likelihood, p is the number of parameters in the model, and n is the number of observations). Modeling was started from the normal distribution (BCPE with L=1 and T=2) and extended to the Box-Cox normal (BCPE with T = 2, also called LMS method of distribution where L is the skewness, M is the median, and S is the coefficient of variation) or full BCPE, if needed. In choosing the "best" model, the main emphasis was settled to the plot of fitted percentiles with observed percentiles. Usually, the BIC information criterion was found as being more applicable than AIC or GAIC, possibly due to the large numbers of observations.

Finally, a normal distribution assumption for height was obtained in the height-for-age analysis. Growth curves for height-for-age were depicted as the mean (M) and mean plus or minus two standard deviations which covered the 2.3th, 50th and 97.7th percentiles. Response variables (BMI and weight) assumed as being a normal Box-Cox distribution. BMI, in the BMI-for-age analysis, was described in terms of the 3rd, 10th, 50th, 90th, and 97th percentiles and the percentiles passing through BMI values of 16, 17, 18.5, 25, and 30 at age 18 years; the widespread method by Cole to define various grade of thinness, overweight and obesity for Finnish children (135,136). Median (the 50th percentile) and 3rd, 10th, 90th, and 97th curves were reported from the analysis of weight-for-length/height.

4.1.3 Height distance from target height

In all 26,636 healthy subjects (12,895 girls, 13,741 boys) that were collected for height-for-age reference database comprised the TH reference population data. The subjects of the study group older than 15 years and with less than 1.0 cm height gain during the last follow-up year were considered as having reached their adult height (AH) (n = 3,481 girls and 886 boys). Mid-parental height (MPH) was the mean of parental heights, corrected for sex (-6.8 cm for girls and +6.8 cm for boys) and converted to SDS by using the former Finnish growth reference (from subjects born 1954-1972) (2), which was considered to better reflect the growth in the parents than the new reference (data from subjects born 1983 – 2009).

Firstly, the two commonly used TH formulas were compared to determine which achieved the most precise estimate of the AH in the reference population. The formula developed by Wright et al. is based on the regression line between MPH SDS and AH SDS (132). The formula developed by Hermanussen & Cole (133),TH SDS = 0.72 * (paternal

height SDS + maternal height SDS) / 2, has been recommended by the international consensus statement for the diagnosis and treatment of children with idiopathic short stature(153). It is based on correlation coefficients between parental and offspring height SDSs and parental height SDSs. Secondly, the differences between height SDS and TH SDS were calculated in the reference population in order to define age-specific reference values for height SDS distance from TH SDS using both TH formulas.

Paired samples t-test was used to test the difference between the two TH formulas.

4.1.4 Growth rate by age

Calculation of the reference values for normal growth velocity was based on longitudinal growth data of the height reference population (height rate by age) and weight reference population (BMI rate by age). Variation in the growth rate over time was based on the fact that the distribution of the change in height SDS and BMI SDS at a fixed age interval is normally distributed with zero mean and SD of $\sqrt{(2*(1-r))}$, in which r is the correlation coefficient between the height SDS and BMI SDS measurements at the ends of the interval (103). As the data were not measured at fixed ages, age groups were formed in order to obtain approximations for the correlations for fixed age intervals. Two different age classifications were used according to the routine measuring schedule adopted in primary care in order to utilize the data as exactly as possible: monthly until one year and yearly for whole age period rounding the age to the nearest integer (month or year). Then the correlations were calculated for all the possible pairs of age groups, and modeled by regression analysis in which the dependent variable was their Fisher's transformation $z = 0.5*\log((1+r)/(1-r))$. The explanatory variables were the group averages of the difference and average of the pair of ages and/or some transformations of these values, if needed, to better capture the dependence structure between the correlation and age (154). In addition, separate models for two different age classifications were created. These four reported regression models can be used to predict the value of a correlation for any pair of observations using the back transformation formula $r = (\exp(2*z)-1)/(\exp(2*z)+1)$ for the predicted value of z. With the known predicted value of correlation, the predicted value of SD for change can also be calculated by using the above SD formula. The standardized value of the change in height SDS and BMI SDS is then the actual change divided by its predicted value of SD. In the normal population, it is normally distributed with a mean of 0.0 and SD of 1.0. In order to depict the normal variation of the growth rate over time, estimates of SD curves for different time intervals were plotted from each model. The goodness-of-fit for the regression model was assessed by creating different residual plots and plotting fitted curves for SDs together with corresponding data points. Parameter estimates were used to define formulas for growth rate reference values that are presented in Table 5A (height SDS aged 0 – 1 years), Table 5B (height SDS aged 1 – 12 years) and Table 5C (BMI SDS aged 2 – 12 years) for girls and boys. These population-based cut-off values for growth rate are scalable for age without any limitation of fixed time intervals.

4.2 GROWTH DISORDER COHORTS

4.2.1 Turner syndrome cohort

Longitudinal height data including 2,184 measurements for 136 girls with TS (born between 1978 and 2009) were collected from three Finnish University Hospitals (Helsinki, Kuopio and Tampere). TS girls were identified from the hospitals' patient registry according to the ICD-10 code (Q96). Clinical data including gestational age at birth, birth size, longitudinal growth data, parental heights, karyotype, the date of TS diagnosis, associated disorders, treatments, and medications were recorded. Twelve TS girls were excluded from the study population: three girls with type I diabetes, one with a malignant tumor, one with

Table 5. Regression formula with Fisher backtransformation and standard deviation formula for height SDS change at different ages, on functions of the mean age (mage) and age distance (dage) for girls and boys. Formula (Coefficient * Estimate) gives the reference for height SDS changes aged 0 – 1 year (A) and 0 – 12 years (B), and BMI SDS changes aged 2 – 12 years (C).

	GIRLS		**BOYS**	
A	**Coefficient**	**Estimate**	**Coefficient**	**Estimate**
	Intercept	2.1193	Intercept	2.0848
	√dage	-0.6335	sqrt(dage)	-1.1072
	1/√mage	-0.0439	log(mage)	0.0601
	$dage^2$	1.1981	$(dage)^2$	0.3001
	√dage/√mage	-0.5424	$1/(mage)^2$	0.0016
	1/√mage*$dage^2$	-0.9754	sqrt(dage)*log(mage)	0.3938
B				
	Intercept	2.4330	Intercept	1.9251
	√dage	-0.0636	sqrt(dage)	-1.5671
	1/√mage	-0.1268	1/mage	-0.1977
	$mage^3$	0.0072	$mage^3$	-0.0001
	√dage/√mage	-1.223	sqrt(mage)	0.4186
	√dage*$mage^3$	-0.0003	sqrt(dage)*$mage^3$	-0.0007
	$mage^3$*ln(mage)	-0.0028	sqrt(dage)*sqrt(mage)	0.4304
C				
	Intercept	1.3835	Intercept	1.3901
	√dage	-0.7729	√dage	-0.5144
	ln(mage)	0.3614	mage	0.0870
	√dage*ln(mage)	0.1248		

hyperinsulinism and seven because of missing parental heights. The remaining TS cohort comprised of 124 (91.2 % of the original cohort) girls and their 2,020 height measurements (Table 6). All the TS girls were measured in the standard way with calibrated equipment by specially trained nurses during scheduled, routine visits at well-baby clinics, school health care or control visits at the hospital outpatient clinics. Potentially false measurements, typing errors, missing values, or duplicate recordings were detected in the longitudinal height data using scatter plots and then either corrected or excluded. Height data were used only until the start of any growth promoting therapy. Height was converted to z-scores in the new Finnish growth reference (I).

4.2.1 Celiac disease cohort

Children aged 0-16 years with CD were identified in patient registries of three University Hospitals in Finland (Helsinki, Kuopio and Tampere) according to International Classification for Diseases version 10 code for CD (K90.0) and clinical and auxological data were collected retrospectively from the patient files. In all cases, the diagnosis of CD was based on the histological evaluation of duodenal biopsies conducted by a pathologist. The biopsy specimens were classified as having either moderate, subtotal or total villous atrophy. In five cases, the degree of villous atrophy was unavailable. Age at diagnosis, preceding symptoms, laboratory results [hemoglobin, total immunoglobulin A (IgA), and IgA transglutaminase (tTG) and endomysium (EMA) antibodies], and histological data were registered. Growth data were collected until the time of diagnosis. Height and weight measurements were transformed into z-scores according to the new Finnish growth reference (I). Potentially false measurements, typing errors, missing values, or duplicated recordings were evaluated by scatter plots, and then either corrected or excluded.

Chi² -test was used to test the differences between girls and boys for symptoms and histopathological findings, and independent samples t-test for growth and laboratory findings. The general linear model for repeated measurements was used for testing the difference of HSDS against the reference population mean height.

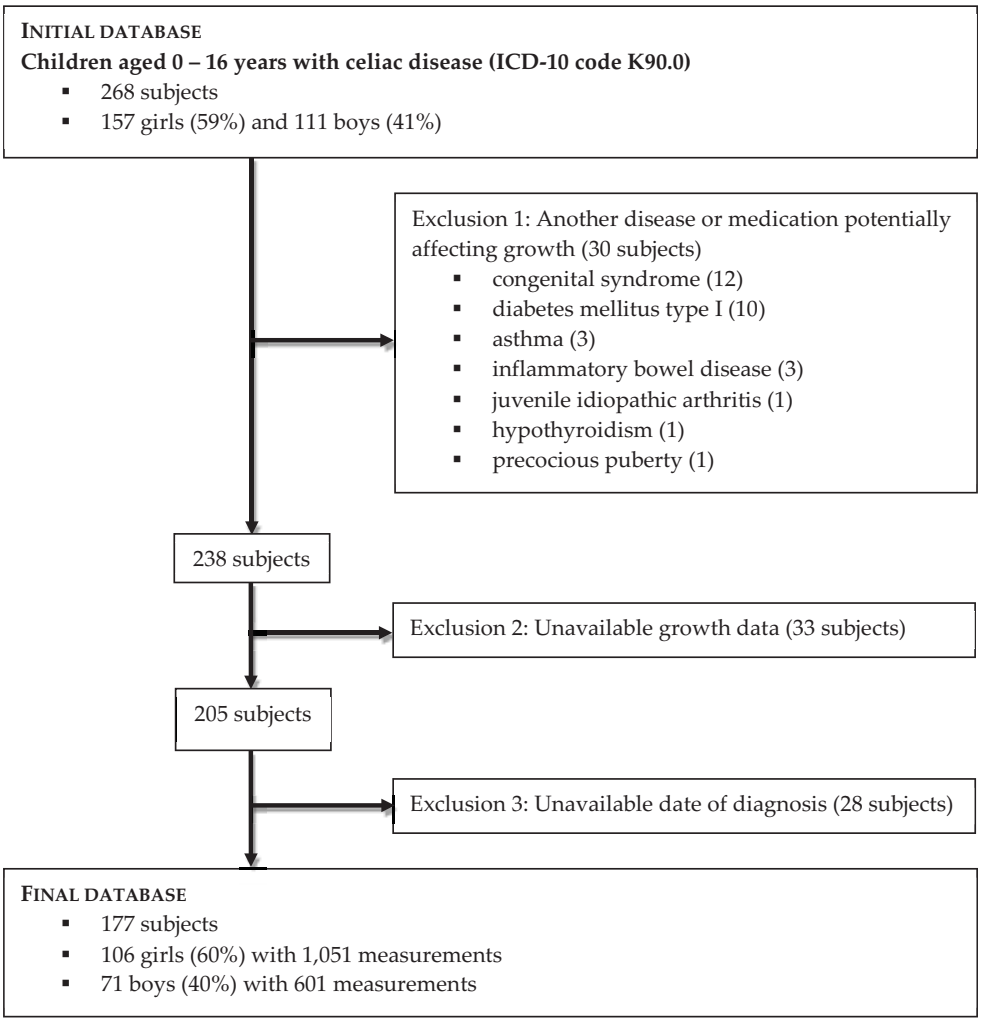

Figure 9. Flow chart for celiac disease cohort.

The initial study cohort consisted of 268 children (59% girls) (Figure 9). The following exclusion criteria were applied: another disease or medication possibly affecting growth (n = 30), unavailable growth data (n = 33), and the absence of the date of CD diagnosis (n = 28). After excluding these cases, the final study cohort consisted of 177 children (106 girls and 71 boys with 1051 and 601 height and weight measurements prior to diagnosis, respectively).

The characteristics of the CD patients are presented in Table 7. Altogether 60 % of the patients were girls ($P < 0.01$). The median age at diagnosis was 6.2 years (range 0.9 – 15.9) in girls and 7.1 years (0.8 – 16.1) in boys (P=n.s.). At the time of diagnosis 33% of the CD children were asymptomatic and the most common symptom preceding the CD diagnosis was recurrent abdominal pain in 27% of children. Diarrhea or loose stools was found in 12 % and constipation in 4% of the patients. Diarrhea with abdominal pain was more prevalent in boys ($P < 0.05$). Histopathological findings showed a more severe grade of

atrophy in boys with a total villous atrophy in 23 (32%), in comparison to 15 (14%) girls (P < 0.01). The majority of CD children had an increased level of IgA antibodies to tTG (mean 103 U/mL in girls and 133 U/mL in boys, P = n.s.) and EMA (titers 767 and 992, P = n.s.). IgA-tTG and EMA antibodies were in the normal range in nine patients and two of these children had also total IgA deficiency. At the time of diagnosis, hemoglobin was below the age-specific reference range in 31% of CD children (Table 7).

In the CD cohort at the time of diagnosis, the mean values of HSDS and BMI SDS were -0.45 (SD 1.08) and -0.25 (1.23) in girls and -0.58 (1.17) and -0.44 (1.08) in boys, respectively (Table 5). Overall, girls with CD were shorter than healthy children at 2 years and in boys at 1 year before diagnosis of CD was made (*P < 0.05)* (Figure 10). Differences in BMI-for-age between the CD patients and healthy children were not statistically significant for either girls or boys (data not shown).

4.2.3 Statistical analyses

The evaluation between multi-ethnic and population specific growth references was performed with longitudinal height data of 124 Finnish TS girls (60 with karyotype 45,XO) containing 2,020 measurements that were assessed either by using the WHO charts (20) or new Finnish growth reference (I). The accuracy of both growth references for detecting growth patterns associated with TS was studied by calculating the cumulative percentage of TS girls with at least one measurement either below the 3rd (screening specificity 97%) or the 1st (specificity 99%) height-for age percentile.

Analyses for diagnostic accuracy of new Finnish growth references for target conditions (TS and CD) were performed with six growth screening parameters:

1. Height-for-age in comparison to the population mean (HSDS rule)
2. TH, i.e. the maximum HSDS distance from TH SDS (TH SDS rule)
3. Change in height rate, i.e. the maximum change in height SDS over time (ΔHSDS rule
4. BMI-for-age in comparison to the population mean (BMI SDS rule)
5. Change in weight rate, i.e. the maximum change in BMI SDS over time (ΔBMISDS rule),

that were evaluated one by one and in combination (6. Combination rule). The first three were combined for TS cohort, and all five for CD cohort, respectively.

First, the individual probability for abnormal growth screening (using HSDS, TH SDS, ΔHSDS or the combination rule for TS cohort, and HSDS, TH SDS, ΔHSDS, BMI, ΔBMISDS and combination rule for CD cohort) were calculated for each girl in the TS cohort and in each child in the CD cohort, and for the reference population using logistic regression. Secondly, these probabilities were used to assess the diagnostic accuracy of growth screening. The diagnostic accuracy was depicted by area under the curve (AUC) –values from Receiver Operating Characteristic (ROC) curves against the reference population. Thirdly, the optimal cut-off points (OCP) for each screening rule were defined so that sensitivity and specificity of the rule obtained the maximal values (OCP was chosen at the point of maximum of sensitivity^2 + specificity^2). The cumulative diagnostic performance of each screening rule was also evaluated by age.

Table 6. Characteristics of the 124 girls with Turner syndrome.

	Turner 45,XO karyotype		Turner Other karyotypes		Turner All	
Sample size, n	60		64		124	
Number of measurements, count	980		1040		2020	
Number of measurements per girl, mean (SD)	16.3	(7.14)	16.3	(6.95)	16.3	(7.01)
Height SDS[a], mean (SD), all measurements	-2.24	(0.80)	-2.07	(1.08)	-2.15	(0.96)
Weight for height SDS[a], mean (SD), all measurements	-0.02	(1.05)	0.01	(1.40)	-0.01	(1.25)
BMI for age SDS[a], mean (SD), all measurements after 2 y	0.02	(0.88)	0.05	(1.32)	0.03	(1.14)
Gestational age (weeks) (n=91)[d], mean (SD)	38.9	(1.71)	38.9	(2.34)	38.9	(2.04)
Birth length (cm) (n=91), mean (SD)	47.3	(1.94)	47.6	(2.99)	47.5	(2.53)
Birth weight (kg) (n=91), mean (SD)	2.99	(0.49)	3.03	(0.65)	3.01	(0.57)
Birth length SDS[b] (n=91), mean (SD)	-1.23	(0.98)	-0.90	(1.32)	-1.07	(1.17)
Birth weight SDS[b] (n=91), mean (SD)	-1.04	(1.17)	-0.96	(1.25)	-1.00	(1.20)
Paternal height SDS[d], mean (SD)	0.17	(0.95)	-0.17	(1.08)	-0.01	(1.03)
Maternal height SDS[d], mean (SD)	0.07	(0.92)	0.02	(1.04)	0.05	(0.98)
Mid -parental height SDS[c], mean (SD)	0.12	(0.71)	-0.08	(0.76)	0.02	(0.74)
Age at diagnosis (years) (n=118)[e], median (range)	0.0	(0-17.0)	5.3	(0-15.9)	3.6	(0-17.0)
Perinatal diagnoses, count	31		12		43	
Karyotype, n (%)						
45,XO	60	(100)			60	(48)
45,XO and 46, XX			13	(20)	13	(11)
45,XO and (46,X,iX or 46,X,idic(X))			10	(16)	10	(8)
46,X, iX or 46, X, idic(X)			5	(8)	5	(4)
45,XO/47,XXX			4	(6)	4	(3)
Other			32	(50)	32	(26)

[a]Finnish growth reference 1983-2008 (I), all measurements
[b]New Finnish growth references for birth size (155)
[c]Finnish growth reference 1959-71 (2)
[d]Not found for 33 TS girls
[e]Not found for 6 TS girls

Table 7. Clinical characteristics at diagnosis in 177 children with celiac disease.

	Girls	**Boys**
Total, count (%)	106 (60)	71 (40)
Age at diagnosis (years), median (min-max)	6.2 (0.9–15.9)	7.1 (0.8–16.1)
Height and weight measurements, count	1051	601
Height and weight measurements per child, mean (SD)	9.9 (6.0)	8.5 (4.8)
Presenting symptoms, count (%)		
Diarrhea and abdominal pain	20 (19)	25 (35)
Constipation and abdominal pain	10 (9)	2 (3)
Only abdominal pain	28 (26)	11 (16)
Asymptomatic	30 (28)	18 (25)
Not known	18 (17)	15 (21)
Histological findings in duodenal biopsy, count (%)		
Moderate villous atrophy	39 (37)	22 (31)
Subtotal villous atrophy	47 (44)	26 (37)
Total villous atrophy	15 (14)	23 (32)
Not known	5 (5)	0 (0)
Laboratory findings, median (min-max)		
IgA-tTG (U/mL)	100 (10–300)	100 (9–1,110)
IgA-EMA (titer)	250 (5–5,000)	250 (10–10,240)
Blood Hb (g/L)	122 (87–139)	122 (80–161)
Height-for-age SDS[a], mean (SD)	-0.45 (1.1)	-0.58 (1.2)
BMI-for-age SDS[a], mean (SD)	-0.25 (1.2)	-0.44 (1.1)
Height distance from TH SDS, mean (SD)	-0.57 (1.2)	-0.67 (1.1)
Target height (TH) SDS[b], mean (SD)	-0.05 (0.6)	-0.06 (0.8)

[a]In comparison to the new Finnish growth reference (I)
[b]TH formula 0.791 x mean parental height (MPH) SDS – 0.147 for girls and 0.886 x MPH SDS – 0.071 for boys (III)

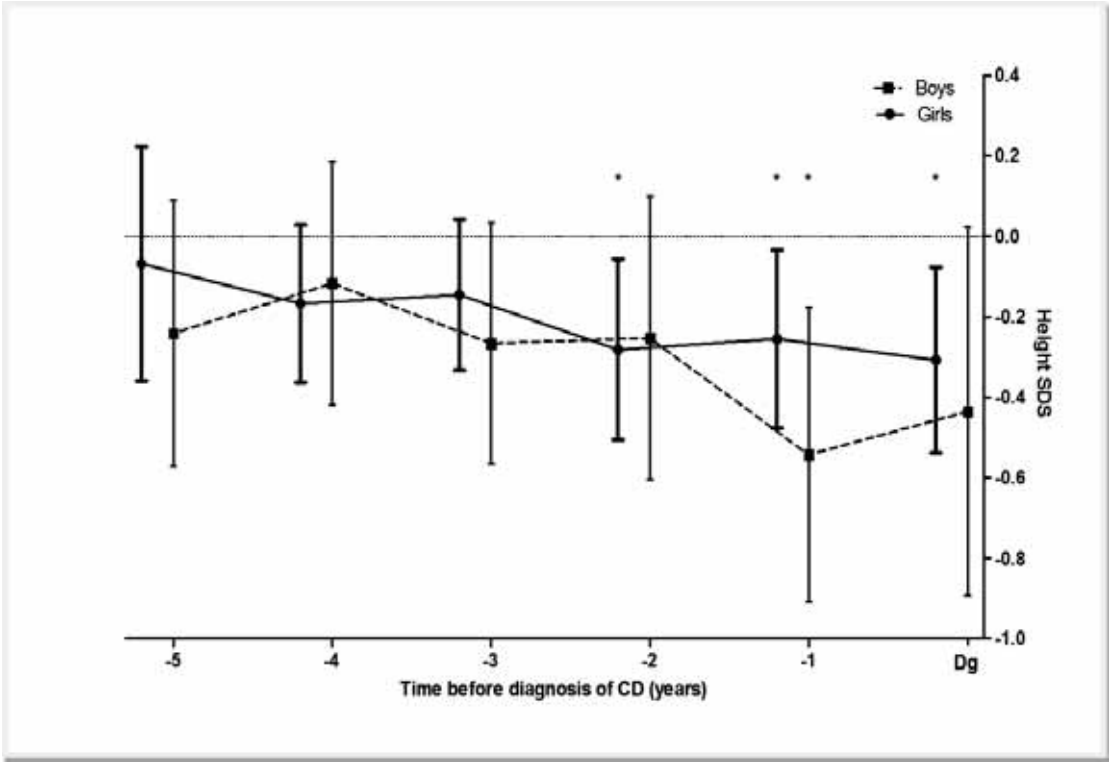

Figure 10. Mean height SDS (95% CI) in girls (solid line and circles) and boys (dashed line and squares) with celiac disease 0 – 5 years prior to the diagnosis in comparison to population based reference (I). The asterisks indicate statistically significant difference ($P < 0.05$)

4.3 AUTOMATED GROWTH MONITORING PROGRAM

The prospective one-year AM intervention was performed in the primary care between March 2008 and February 2009. Data collection for AM intervention year was performed as a part of the growth reference study for height reference (Figure 8). The whole child population between 0.01 and 12 years was included in the study and covered by the free-of-charge national health monitoring program (150). One year before the AM intervention year (between March 2007 and February 2008) was used as the control year with SM strategy, to obtain a comparator for the evaluation of the change in effectiveness.

The Finnish child population had been screened from infancy to early adolescence for abnormal linear growth according to the nationwide SM strategy (Table 2) (2-4). In this programme, if the primary care nurse considers the growth to be abnormal, then she/he consults the primary care physician who performs an assessment or baseline investigations and may refer the child to secondary care.

During the control year an average of 32,718 children were measured 76,926 times, and during AM intervention year 32,404 children were measured 77,409 times (see Figure 26). The growth of 22,135 (68.3%) children measured during the AM intervention year had been assessed in the control year.

4.3.1Automated growth monitoring intervention

The one-year AM intervention was run concurrently with the ongoing SM strategy, and is presented in Figure 11. The AM included two additional automated steps: firstly, the longitudinal growth data of each measured child were automatically analysed by the computerised screening algorithms integrated into the EHR system. Secondly, if the

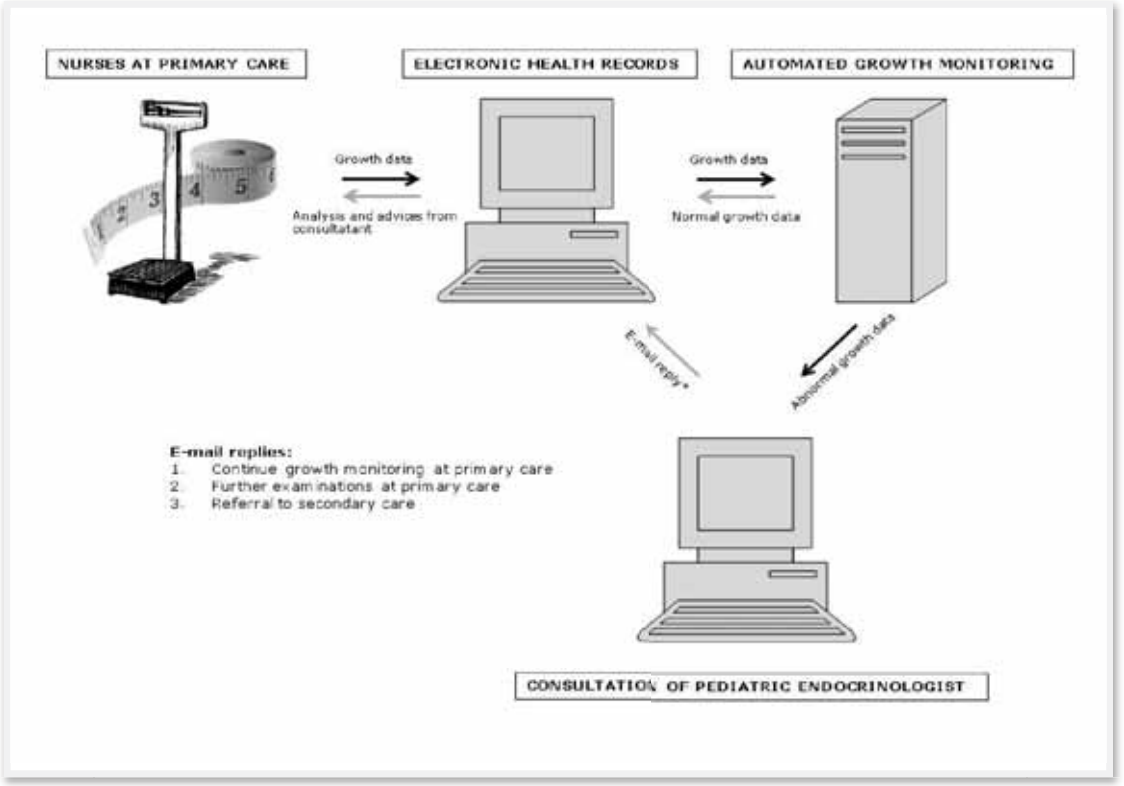

Figure 11. The one-year automated growth monitoring intervention process: 1. Measuring children and imputing growth data to electronic health records, 2. Automated growth monitoring, 3. Consultation of pediatric endocrinologist, 4. Consultant's advice to the primary care.

automated screening result was abnormal, the individual's growth and clinical data were automatically transferred as an online growth consultation to a paediatric endocrinologist in secondary care. An e-mail was then sent to the primary care nurse which included an analysis of the growth pattern and advice for further management. During the AM intervention, a referral to secondary care may have originated from the nurse and primary care physicians' own interpretation of the child's growth pattern or after the consultation response.

4.3.2 Analyses for effectiveness of automated growth monitoring

The primary effectiveness outcomes were the referral rates for suspected abnormal growth, the diagnostic yield of growth disorders, and the delay in their diagnosis during the AM intervention year versus the control year (detailed in Figure 12). Children with previously diagnosed growth disorders were filtered out from the study population before the study, and only previously undiagnosed growth disorders were registered by using the European Society for Paediatric Endocrinology classification of primary and secondary growth disorders and idiopathic short stature (ISS) (82).

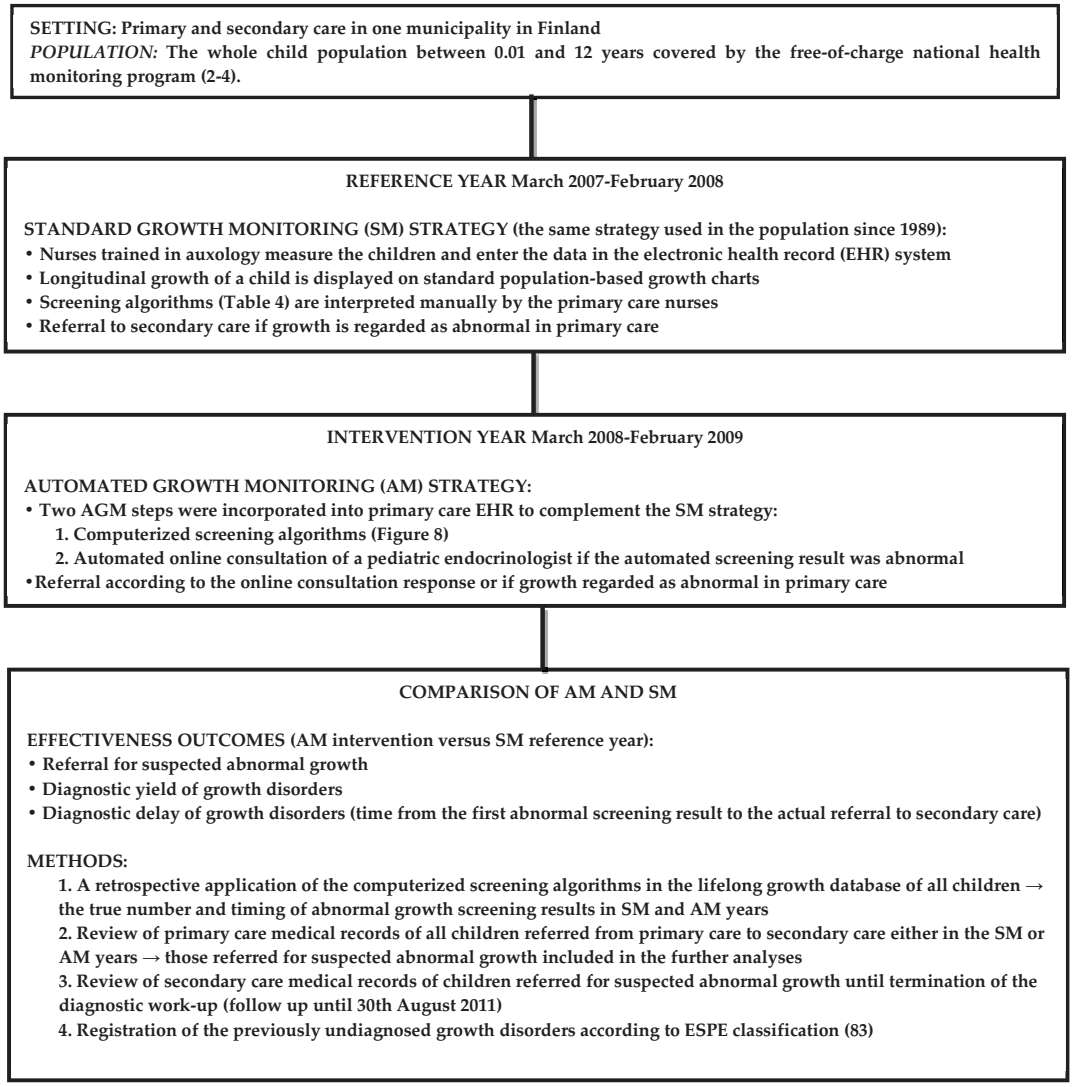

Figure 12. Automated growth monitoring (AM) intervention that was integrated into an electronic health record during the AM. Screening algorithms are presented in Table 4 on page 19.

The absolute risks (risk ratios; RRs) for referral for abnormal growth and the RRs for rate of new growth disorder diagnoses were calculated. The diagnostic yield was defined as the number of measured children per single newly diagnosed growth disorder. Poisson regression was used to assess if the number of referrals or new cases of growth disorders differed between the AM and control years. RRs in the two years were compared by the confidence interval (CI) analyses using 95% CI. The Fisher's exact test was used in the comparison between the proportions of children in the SM and AM intervention years.

Excel 2007 (Microsoft Corporation, Burbank, WA, United States), SPSS version 19 (IBM Corporation, Armonk, NY) and R statistical software were used in the analyses conducted in this study. P values less than 0.05 were considered statistically significant.

4.4 APPROVAL OF ETHICS COMMITTEE

Permission for the study was obtained from Espoo Municipality Institutional Review Board (I & V) and the ethics committee of the Kuopio University Hospital (II, III & IV), and Hospital for Children and Adolescents, Helsinki University Hospital (V). No contact with the study subjects was considered necessary since the data were analysed anonymously.

5 Results

5.1 GROWTH REFERENCES

Figure 13 shows the new Finnish growth reference 1983–2008 for length/height-for-age in comparison with the old growth reference 1956–1973. The mean birth lengths in the reference 1983–2008 population were 50.3 cm in girls and 51.1 cm in boys compared to 50.2 cm and 50.7 cm in the old reference, respectively. The mean birth lengths of full-term babies in the new Finnish growth references for birth size from the year 2013 is 50.1 cm in girls and 51.0 cm in boys (149) suggesting that the population selected for the new length/height reference is a fair representation of the contemporary Finnish population. The mean adult height of girls increased by 1.9 cm (from 165.3 cm in the reference 1956–73 to 167.2 cm in the reference 1983–2008 population); the mean adult height between the cohorts for boys increased by 1.8 cm from 178.9 cm to 180.7 cm, respectively.

In the growth reference 1983-2008, girls and boys at the age of 18 were 1.4 and 1.1 cm taller, respectively than girls and boys in the reference 1956-73 at the age of 20 years. This indicates that there still is a positive secular change occurring in adult heights in Finland

5.1.1 Secular trends in height

The growth pattern resulting in the increased adult height had distinct age- and sex-specific features (Figure 14). Between the ages of 0 to 20 years, subjects in the growth reference 1983–2008 were generally taller than subjects in the reference 1956–73; however, the difference was almost nonexistent in boys and negative in girls during infancy (approximately 5 to 11 months of age). In that age range, girls from the 1983–2008 population were, on average, 0.2 cm/0.07 SDS shorter than girls from the growth reference 1956–73. The positive secular change was more substantial in boys at all ages even though the adult height increase was similar in boys and girls (1.8 cm/0.27 SDS and 1.9 cm/0.32 SDS, respectively). The maximum difference in height in boys was seen around the age of 13 years (a 5.6 cm/0.70 SDS increase when compared to the reference 1956–73 population). In girls, the maximum difference between the two reference periods seemed to occur earlier, around at the age of 11.5 years, and was less than that observed in boys (2.8 cm/0.40 SDS).

The total number of length/height measurements from different age groups of the height reference 1983–2008 population and the percentage of measurements outside the mean ±2SD of the existing height reference 1956–73 are shown in Table 8. On average, measurements in girls (3.4%, range 1.2–5.6%) and boys (4.3%, range 1.9%–8.9%) were above +2SD which was clearly different from the expected 2.3% of normally distributed height). The proportion of measurements above +2SD was less than 2.3% in girls aged 4 to 18 months and in boys aged 5 to 10 months. The highest proportions of measurements above +2SD were seen in girls aged 11 to 12 years and in boys aged 12 to 13 years. Only 0.9% of measurements in girls (range 0.4–1.8%) and 0.5% (range 0.1–1.0%) of measurements in boys were below –2SD of the reference 1956–73.

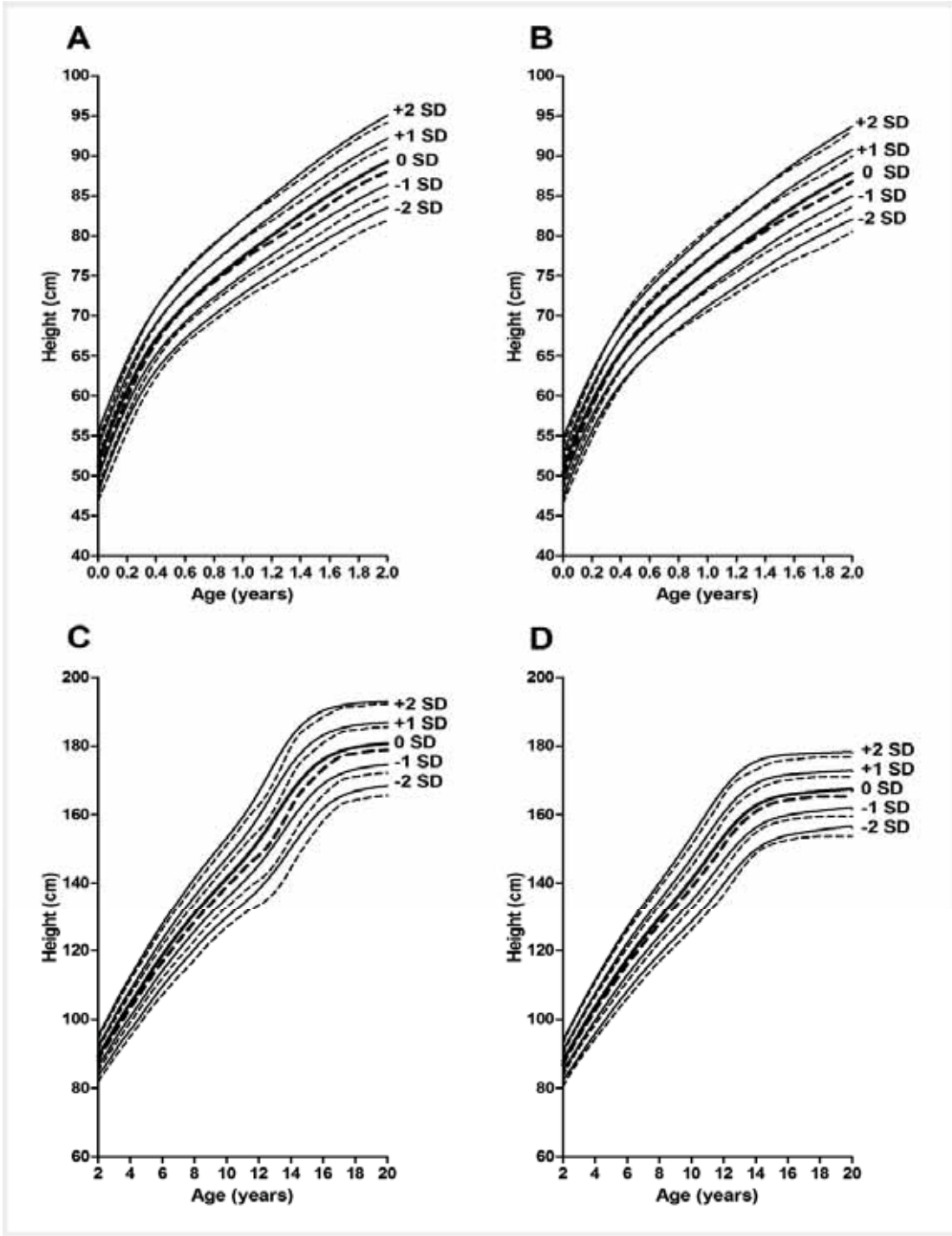

Figure 13. The new Finnish length/height-for-age reference (mean ±2 SD, solid lines). Curves based on 181,785 measurements from 26,636 full-term healthy subjects born between 1983 and 2008 compared to the current Finnish growth reference based on subjects born between 1956 and 1973 (mean ±2 SD, dashed lines). A: boys aged 0–2 years; B: girls aged 0–2 years; C: boys aged 2–20 years; and D: girls aged 2–19 years.

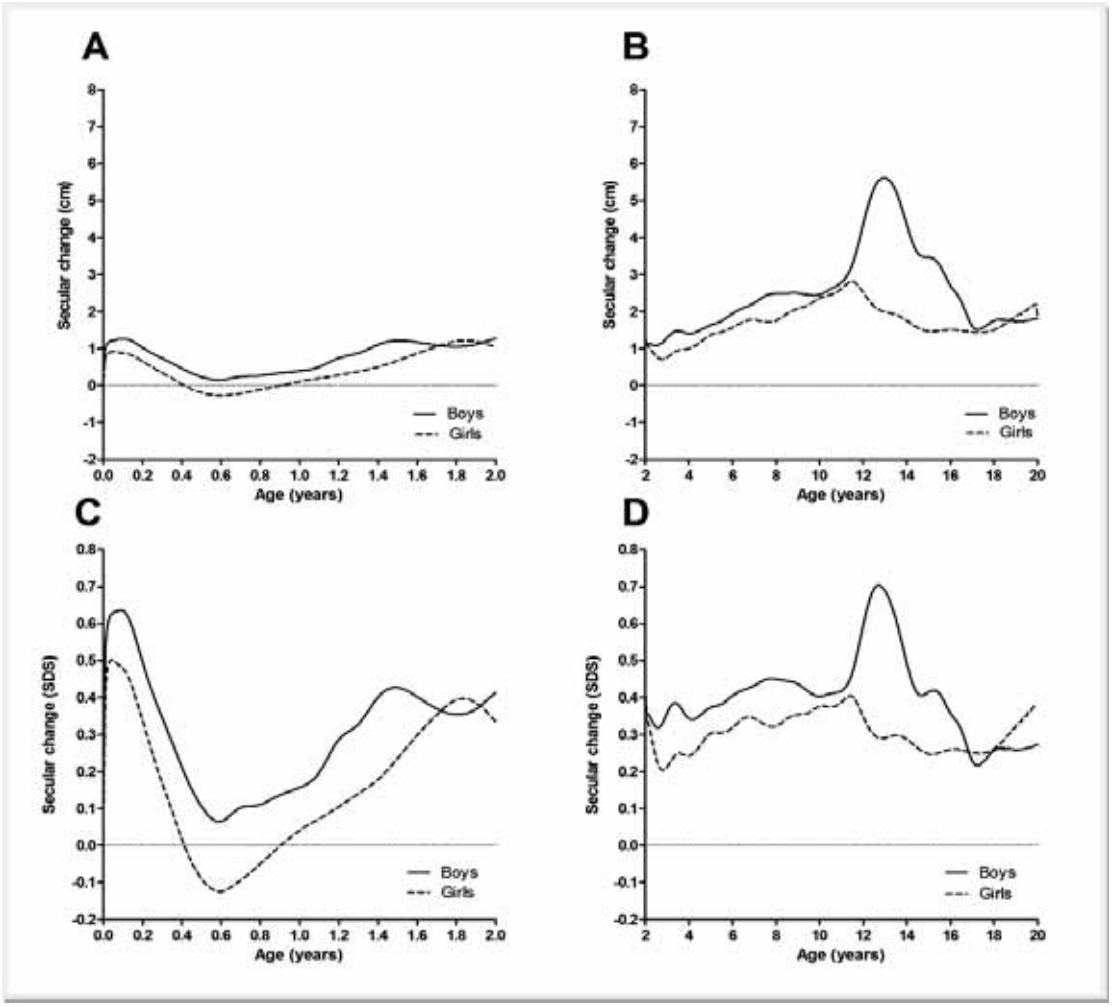

Figure 14. Age- and sex-specific features of the secular change in mean length/height in Finland. Comparison between growth reference 1956–1973 population subjects (those born between 1956 and 1973) and reference 1983–2008 population subjects (those born between 1983 and 2008). Curves indicate differences from the reference 1956–1973 population in: A: mean height in cm from birth to age 2 years; B: mean height in cm from age 2 to 20 years; C: mean height in SD units from birth to age 2 years; and D: mean height in SD units from age 2 to 20 years. Dashed line = girls; solid line = boys.

5.1.2 Multi-ethnic versus population-based growth references

The cumulative percentage (i.e sensitivity) for detecting TS was significantly higher when the population specific growth reference was used (Figure 15). By the age of 2 years, 72% and 55% of all TS girls (81% and 67% of 45,XO girls) had at least one height measurement below the 3rd and 1st percentiles, respectively, in population specific growth reference. In contrast, only 36% and 20% of all TS girls (41% and 23% of 45,XO girls) had a height measurement below these percentiles when the WHO standard was used ($p \leq 0.001$, McNemar's test). From 2 to 5 years, the gap in the cumulative sensitivity between the two growth references grew even wider, especially if the 1st percentile was used as the cutoff (Figure 15).

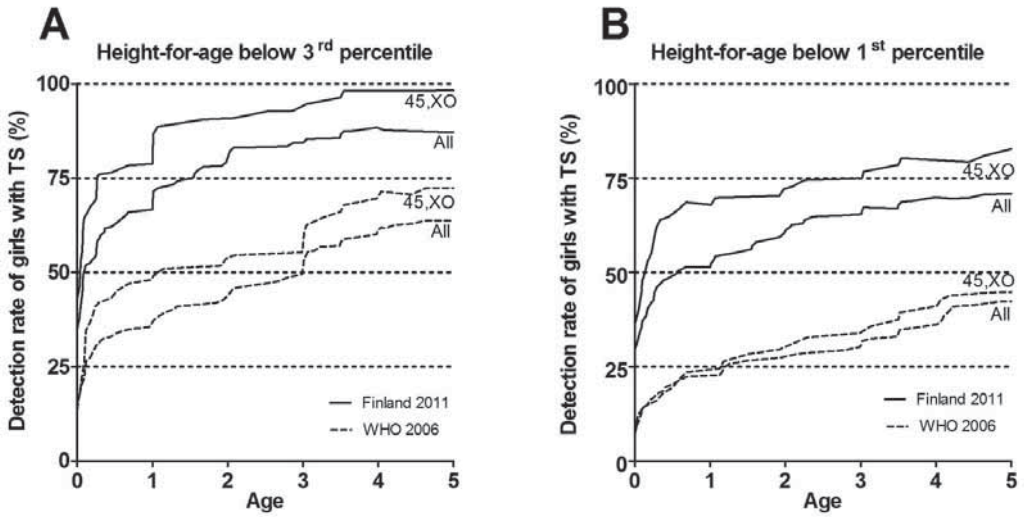

Figure 15. Percentage of girls with Turner syndrome (TS) with height for age less than the third (A) or the first (B) percentile of either the Finnish (upper solid lines) or the World Health Organization (WHO) (lower dashed lines) growth reference for all girls with TS (All, n=124) and those with an XO karyotype (45,XO, n=60).

5.1.3 Weight-for-length/height reference

New median weight-for-length/height percentile (3rd, 10th, 50th, 90th, 97th) curves for girls and boys in the weight reference 1983–2008 population are compared to median curve of the reference 1959–71 population (Figure 16). The median weight-for-length/height curves for both populations were nearly superimposable up to a height of 140 cm (corresponding to a height age of 10 years) in boys and 155 cm (a height age of 12 years) in girls. Subsequently, a slight increase in median weight-for-length/height was observed in reference 1983–2008 population subjects.

5.1.4 BMI-for-age reference

BMI percentile curves (3rd, 10th, 50th, 90th, and 97th) for Finnish children and adolescents aged 2 to 18 years are shown in Figure 17. BMI percentile curves for Finnish children have not been previously published. The median (50th percentile curve) BMI-for-age declined slightly from the age of 2 years until approximately 6 years in both girls and boys and then started to increase. The point at which the BMI values increase is called the 'adiposity rebound' (35). This took place later in the lower percentiles in comparison to the higher values (Figure 17). Median BMI-for-age was slightly higher in boys than in girls between the ages of 2 to 5 years and 8 to 13 years (up to 0.3 kg/m^2). After the age of 15 years, the difference between boys and girls increased rapidly with boys having up to a 1.1 kg/m^2 higher median BMI than girls by the age of 18 years.

Table 8. Number of height measurements in the present population and percentage of measurements < -2SD and > +2SD when compared to the reference population.

		Boys outside the ±2SD range of the old growth reference			Girls outside the ±2SD range of the old growth reference	
	Boys			**Girls**		
Age group	**Count**	**% ≤-2SDS**	**% ≥+2SDS**	**Count**	**% ≤-2SDS**	**% ≥+2SDS**
<1mo	4178	0.3	6.5	3969	0.7	5.3
1-2mo	4943	0.3	6.0	4596	0.4	5.4
2-3mo	3285	0.1	4.5	3161	0.8	3.6
3-4mo	5658	0.3	3.7	5262	0.8	3.1
4-5mo	4230	0.5	3.0	4016	1.1	2.2
5-6mo	4526	0.8	2.1	4310	1.4	1.2
6-8mo	5105	0.7	1.9	4805	1.7	1.3
8-10mo	4500	0.8	1.9	4236	1.7	1.4
10-12mo	3268	0.9	2.4	3233	1.2	1.5
12-18mo	4764	0.6	3.0	4491	1.0	2.0
18-24mo	4010	0.5	4.2	3794	0.5	3.6
2-3y	4195	0.4	4.4	3872	0.4	3.4
3-4y	4004	0.3	4.5	3757	0.5	3.9
4-5y	1473	0.4	4.5	1339	0.8	4.3
5-6y	3609	0.3	5.2	3369	0.5	3.9
6-7y	3386	0.2	4.8	3290	0.6	4.3
7-8y	2405	0.3	5.5	2141	0.7	4.4
8-9y	2689	0.2	6.0	2608	0.6	4.4
9-10y	2648	0.3	5.8	2459	0.5	4.5
10-11y	1504	0.4	4.8	1444	1.2	4.8
11-12y	2621	0.4	5.4	2646	0.8	5.6
12-13y	1993	0.4	8.9	2010	1.4	4.2
13-14y	2443	0.3	8.1	2503	1.8	4.3
14-15y	2071	0.8	4.0	1999	1.3	4.3
15-16y	1566	1.0	3.2	1551	1.2	3.6
16-17y	1824	0.8	2.7	1816	1.4	3.9
>17y	735	1.0	3.0	661	1.2	4.4
Total	**87633**	**0.5**	**4.3**	**83338**	**0.9**	**3.4**

Total number of girls = 12,895 girls; boys = 13,741 boys.

Population includes subjects born between 1983 and 2008; old growth reference includes subjects born between 1956 and 1973 (2-4). Birth measurements are not shown.

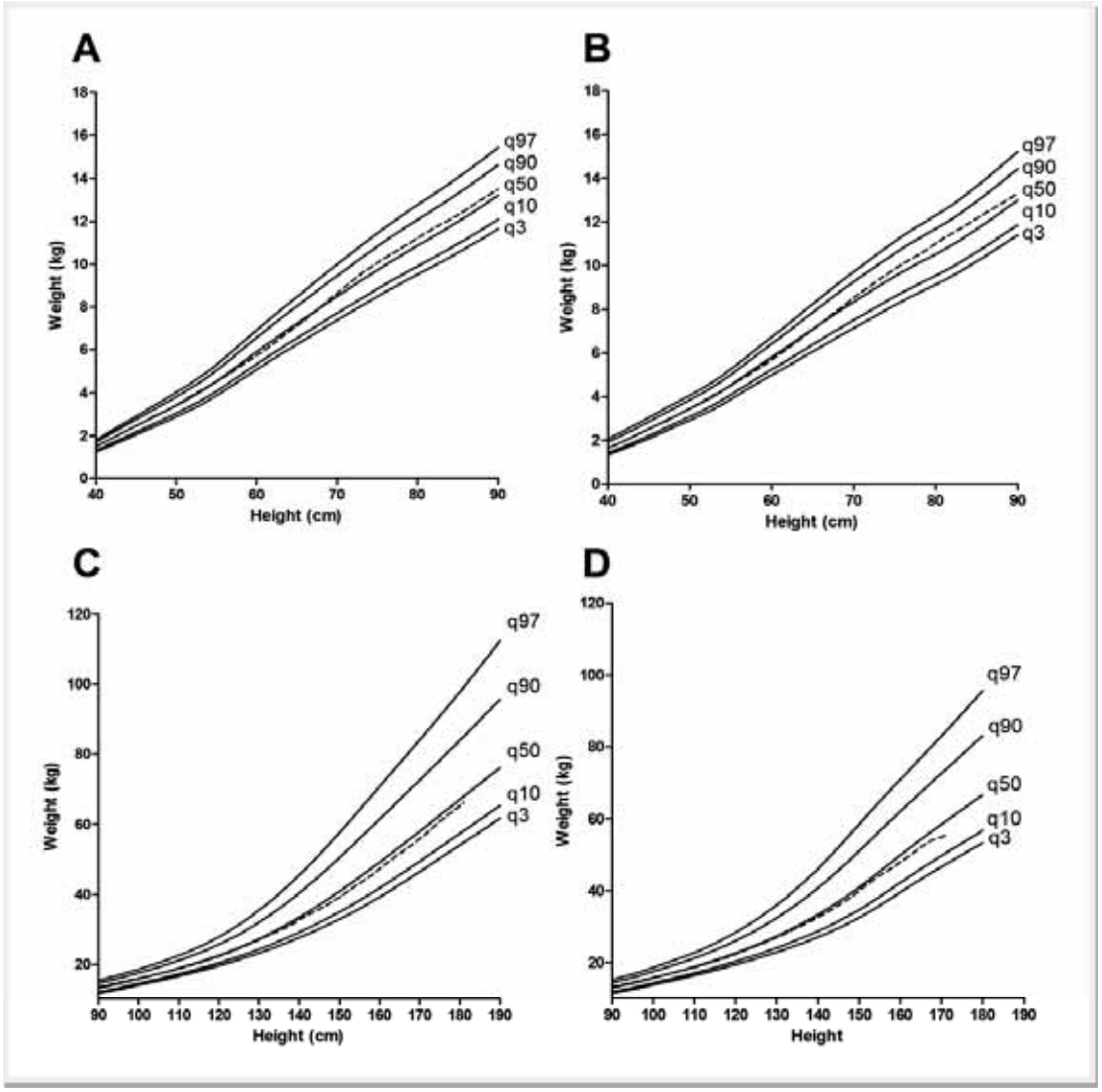

Figure 16. The new Finnish weight-for-length/height percentile (3rd, 10th, 50th, 90th, 97th) curves. Curves based on 428,526 length/height and weight measurements taken from 73,659 healthy subjects in the weight reference 1983–2008 population (those born between 1983 and 2008; solid lines) compared to the median weight-for-length/height curve of the reference 1956–73 population (those born between 1956–1973; dashed line). A: boys 45–90 cm; B: boys 90–180 cm; C: girls 45–90 cm; D: girls 90–190 cm.

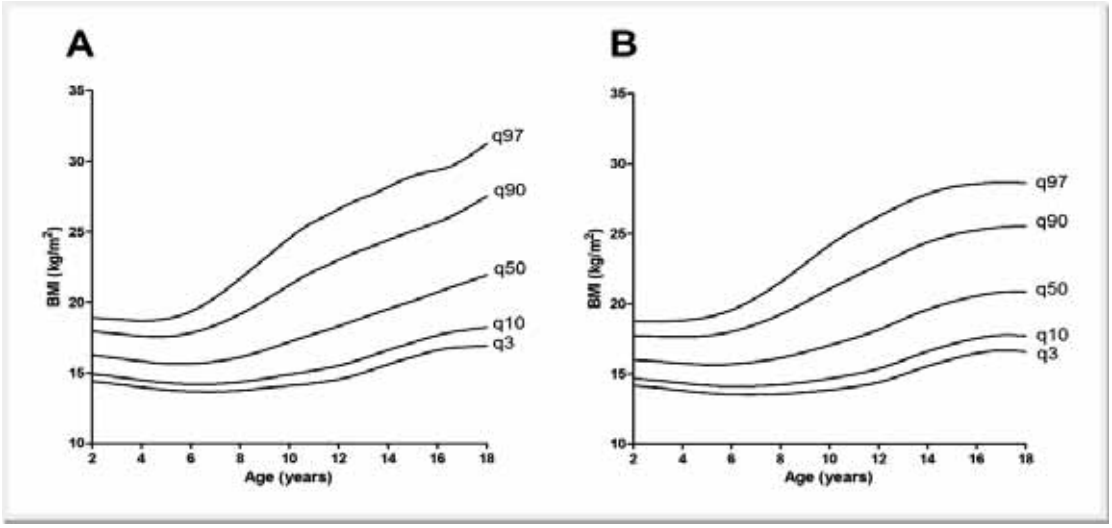

Figure 17. The new Finnish BMI-for-age reference percentile curves. The 3rd, 10th, 50th, 90th, and 97th curves are shown for children and adolescents aged 2–18 years. A: boys; B: girls.

5.2 SCREENING CUT-OFF VALUES FOR ABNORMAL GROWTH

5.2.1 Height-for-age distance from TH and growth rate.

The modified Wright (132) formula in the reference subpopulation with known AHs (n=3,481) resulted in the following TH formulas for boys and girls (Figure 18):

Boys' THSDS = 0.89 * MPH SDS – 0.07
Girls' TH SDS = 0.79 * MPH SDS – 0.15

These were compared to the Hermanussen and Cole formula (133) with respect to the AH SDS and height SDS at ages 15-18 years (Figure 19). The mean (SD) difference between height SDS and TH SDS was 0.00 (0.80) for girls, and 0.00 (0.79) for boys when using the modified formula by Wright et al., and -0.14 (0.81) and -0.07 (0.79), respectively, when using the formula of Hermanussen and Cole (P = not significant for boys, $P \leq 0.05$ for girls) (Figure 18). In addition, the mean difference between AH SDS and TH SDS was significantly smaller when the modified Wright formula was used for girls, and this was true in virtually all age groups from 0 to 12 years ($P \leq 0.05$), and especially in short and tall children (data not shown). As the formula devised by Wright at al. appeared to be more concordant with the AH SDS and childhood height SDS than that of Hermanussen and Cole, it was selected for further use.

Age-specific reference values for height SDS distance from TH SDS were calculated, and cut-offs in 95% and 98% specificity are shown in the Table 9. The cut-off values at a specificity of 95% ranged from 1.5 to 1.9, and the corresponding cut-offs for 98% specificity were 1.8 to 2.3 for both girls and boys in the age groups of 0 to 18 years.

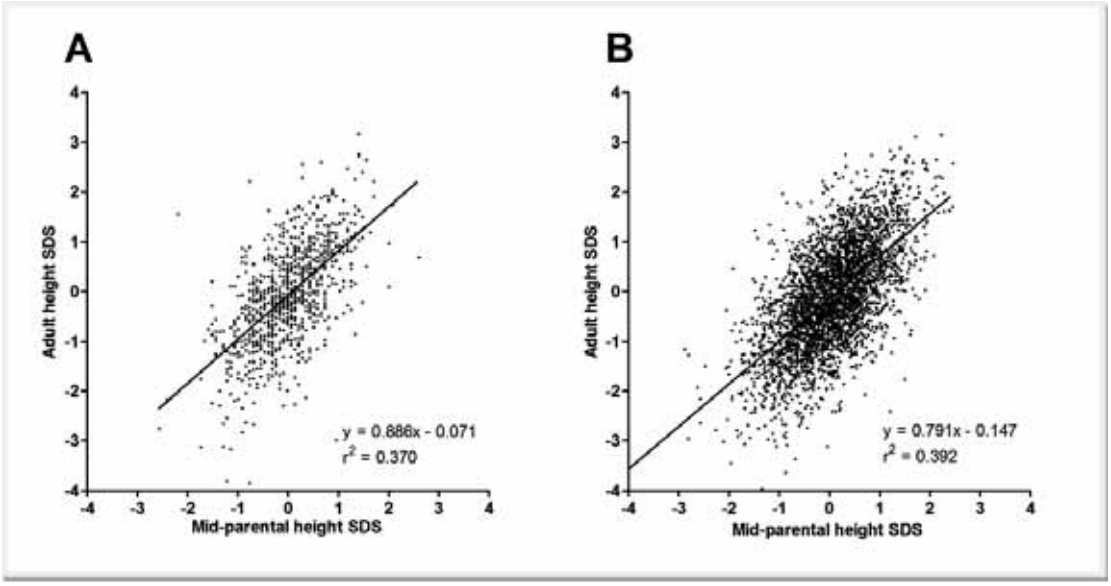

Figure 18. Adult height SDSs of 886 healthy boys and 3,481 girls of the Finnish growth reference population (I) plotted against their mid-parental height (MPH) SDSs. The regression line was used for the modified formula of target height TH SDS = 0.89 * MPH SDS – 0.07 for boys, and TH SDS = 0.79 * MPH SDS – 0.15 for girls.

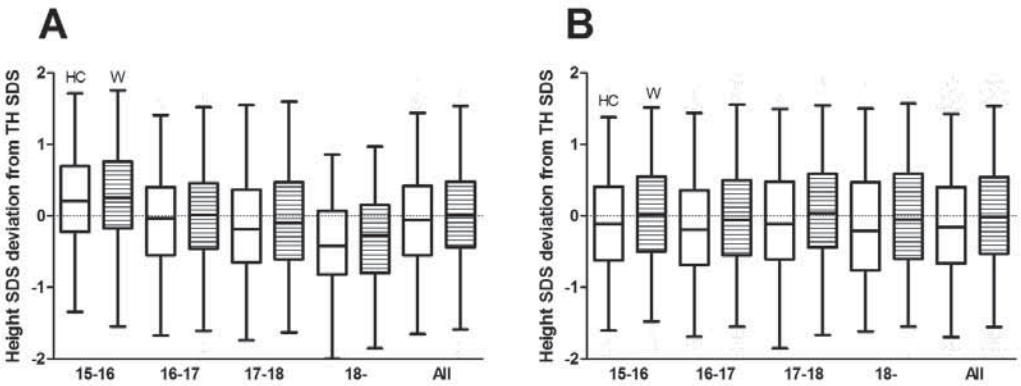

Figure 19. Comparison of the modified target height formula devised by Wright and Cheetham (132) and the formula of Hermanussen and Cole (133) in the reference population. Observed mean HSDS difference from the target height SDS is shown for the boys (A) and girls (B) in the reference population that had reached their AH (B) subdivided into different age groups (years).

Table 9. Age-specific cut-off values (95% and 98% specificity) for height SDS distance from target height (TH) SDS according to the modified TH formula devised by Wright and Cheetham (132) calculated from the reference values shown in Figure 18.

Boys	**Age**								
Specificity	**0-1**	**1-2**	**2-3**	**3-4**	**4-5**	**5-6**	**6-7**	**7-8**	**8-9**
95%	1.9	1.8	1.8	1.7	1.7	1.7	1.6	1.6	1.6
98%	2.3	2.1	2.1	2.0	2.1	2.0	2.0	2.0	2.0
	9-10	**10-11**	**11-12**	**12-13**	**13-14**	**14-15**	**15-16**	**16-17**	**17-18**
95%	1.7	1.6	1.6	1.9	1.9	1.8	1.7	1.6	1.5
98%	2.0	1.9	1.9	2.2	2.3	2.2	2.0	1.8	1.8

	Age								
Girls	**0-1**	**1-2**	**2-3**	**3-4**	**4-5**	**5-6**	**6-7**	**7-8**	**8-9**
95%	1.9	1.8	1.8	1.7	1.7	1.7	1.7	1.7	1.6
98%	2.3	2.2	2.1	2.0	2.1	2.0	2.0	2.0	1.9
	9-10	**10-11**	**11-12**	**12-13**	**13-14**	**14-15**	**15-16**	**16-17**	**17-18**
95%	1.6	1.8	1.8	1.8	1.6	1.5	1.5	1.5	1.5
98%	1.9	2.1	2.2	2.1	1.9	1.8	1.8	1.8	1.8

Reference values for growth velocity (height SDS and BMI SDS) could be calculated between two measurements in free age intervals that are based on regression formula given in Table 5. As an example, cut-off values for height rate (decrease or increase) are shown with 99% specificity at fixed time intervals in the preceding 0.25, 0.5 and 0.75 years for children 0 to 1 years of age, and in the preceding 1, 3 and 5 years in children 1 to 12 years of age, respectively, in Figure 20. Understandably, cut-off values were showed greater tolerance over longer time range, and during infancy and puberty.

Finnish and international (IOTF) percentile curves defining overweight were nearly superimposable in girls with the maximum difference of only 0.7 kg/m^2. In boys, the largest difference (up to -1.2 kg/m^2) between the two overweight curves was seen between the ages of 2 to 6 years with the Finnish overweight curve being lower than the IOTF curve.

The cut-off curves for overweight and obesity (i.e., a BMI of 25 and 30 kg/m^2 at the age of 18 years) were the 87.8th percentile and 98.2nd percentile in girls and the 78.2nd percentile and 95.6th percentile in boys, respectively.

The cut-off curves for grade 1, 2, and 3 thinness (i.e., BMIs of 18.5, 17, and 16, respectively) were at the 17.9th, 5.0th, and 1.3rd percentiles in girls and the 12.1st, 3.3rd, and 1.0st percentiles in boys, respectively

5.2.2 BMI-for-age cut-offs for thinness, overweight, and obesity

Finnish cut-off curves passing through BMIs of 30, 25, 18.5, 17, and 16 kg/m^2 at the age of 18 years (corresponding to obesity, overweight and grade 1, 2, and 3 thinness, respectively) were calculated for Finnish children (Figure 21). A comparison of the Finnish "normal area BMI" (i.e., between grade 2 thinness and overweight) with respect to international data is also provided (135,136).

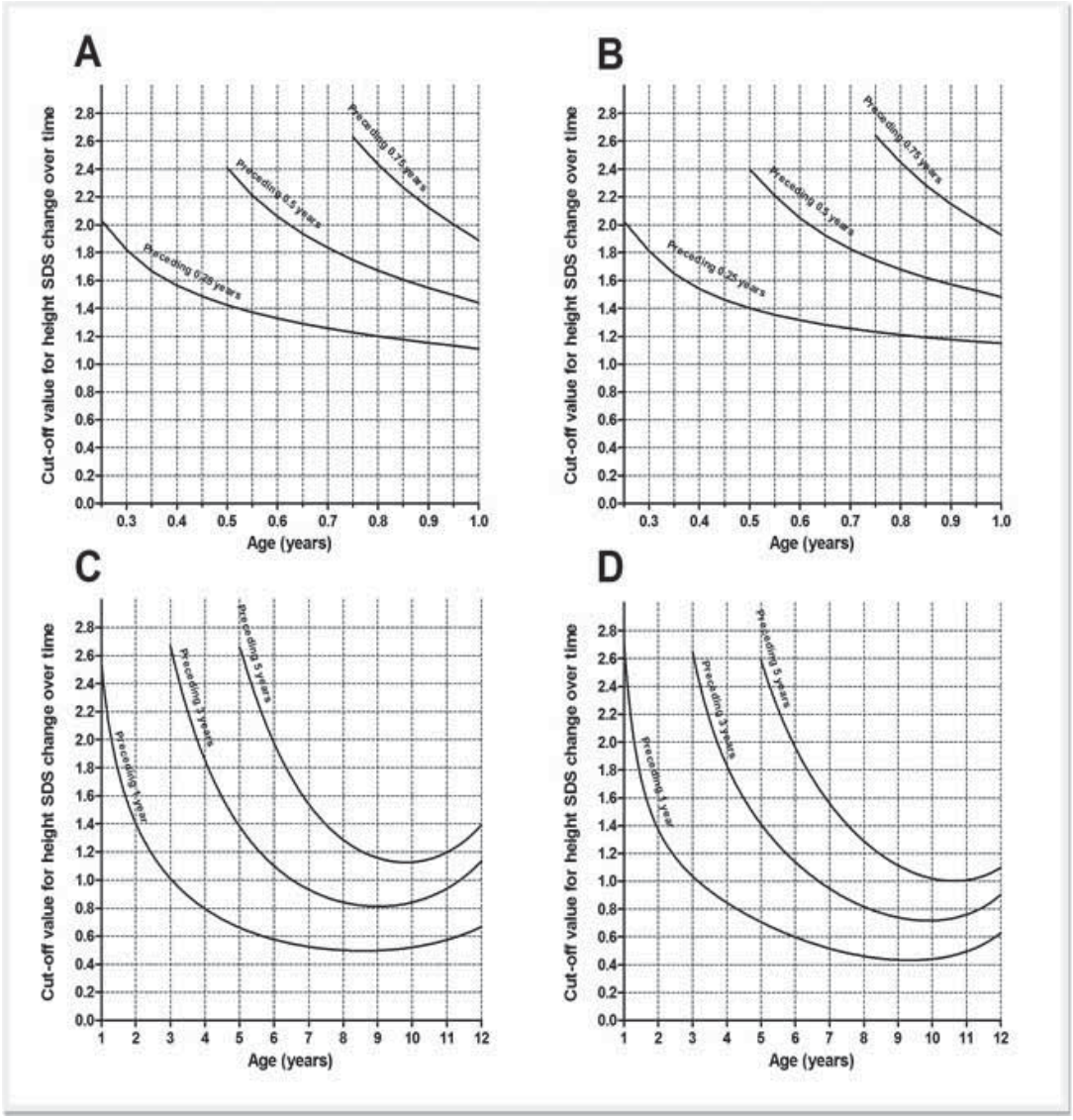

Figure 20. Age-specific cut-off values (99% specificity) for height SDS rate for children aged 0 to 1 year; boys = A, girls = B in the preceding 0.25, 0.5 and 0.75 years, and aged 1 to 12 years; boys = C, girls = D in the preceding 1, 3 and 5 years.

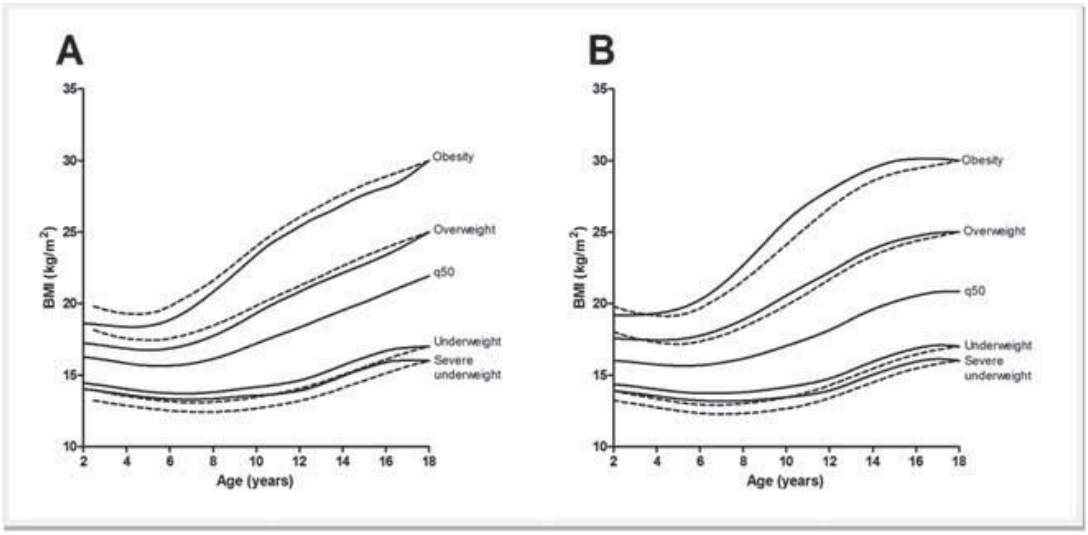

Figure 21. Finnish BMI-for-age percentile curves for grade 3 and 2 thinness, overweight, and obesity. The percentiles passing through BMIs of 16, 17, 25, and 30 kg/m2 at the age of 18 years and the 'normal BMI area' between percentiles of grade 2 thinness and overweight (shaded area) are shown. The corresponding BMI-for-age percentile curves from multi-ethnic data (dashed lines) indicate grade 2 thinness and overweight (International Obesity Task Force international reference) (135,136). A: boys; B: girls.

5.3 GROWTH MONITORING ACCURACY FOR TARGET CONDITIONS

5.3.1 Turner syndrome

With either HSDS rule or TH SDS rules, the screening accuracy was slightly better for 45,XO TS girls than in the whole TS cohort. With the HSDS rule, the AUC -value was 0.98 (95% CI 0.97–1.00) in 45,XO TS girls and 0.97 (0.96–0.99) in all TS girls, and with the TH SDS rule, 0.99 (0.99–1.00) and 0.98 (0.96–0.99), respectively (Figure 22). In contrast, the screening accuracy with the ΔHSDS rule was slightly better for all TS girls than for 45,XO girls with AUCs of 0.72 (0.68–0.76) versus 0.71 (0.66–0.77). ΔHSDS rule displayed a poorer screening accuracy than the HSDS or TH SDS rule alone. Combining the three rules resulted in an excellent screening accuracy with AUCs of 1.00 (0.99–1.00) for 45,XO TS girls and 0.99 (0.98–1.00) for all TS girls, respectively.

The OCP for HSDS rule was observed at -1.92 SDS with the sensitivity of 93% and specificity 93% in whole TS group, and -2.13 SDS with the sensitivity of 95% and specificity of 96% in the 45,XO group. The OCPs values for the TH SDS-rule and the ΔHSDS rule were -2.03 (sensitivity-specificity pair 92%, 94%) and -0.40 (96%, 32%) for all, and -2.65 (98%, 94%) and -0.40 (97%, 32%) for 45,XO TS girls, respectively. When the combination rule was used, OCP (HSDS-rule -2.43, THSDS-rule -1.60 and ΔHSDS rule -1.44) was observed at sensitivity-specificity pairs 97%, 96% for all and 100%, 95% for 45,XO the TS girls.

At all ages, the combination rule provided the highest sensitivity for all TS girls and also for the subgroup of 45,XO girls (Figure 23). By using the combination rule, 85% of all and 93% of 45,XO TS girls were detected by the age of 2 years with 97% specificity, and 68% of all and 76% of 45,XO TS girls with 99% specificity, respectively. Additionally, all the 45,XO girls were detected by the age of 7 years with 97% specificity, and 97% of 45,XO girls by the age of 12 years with 99% specificity.

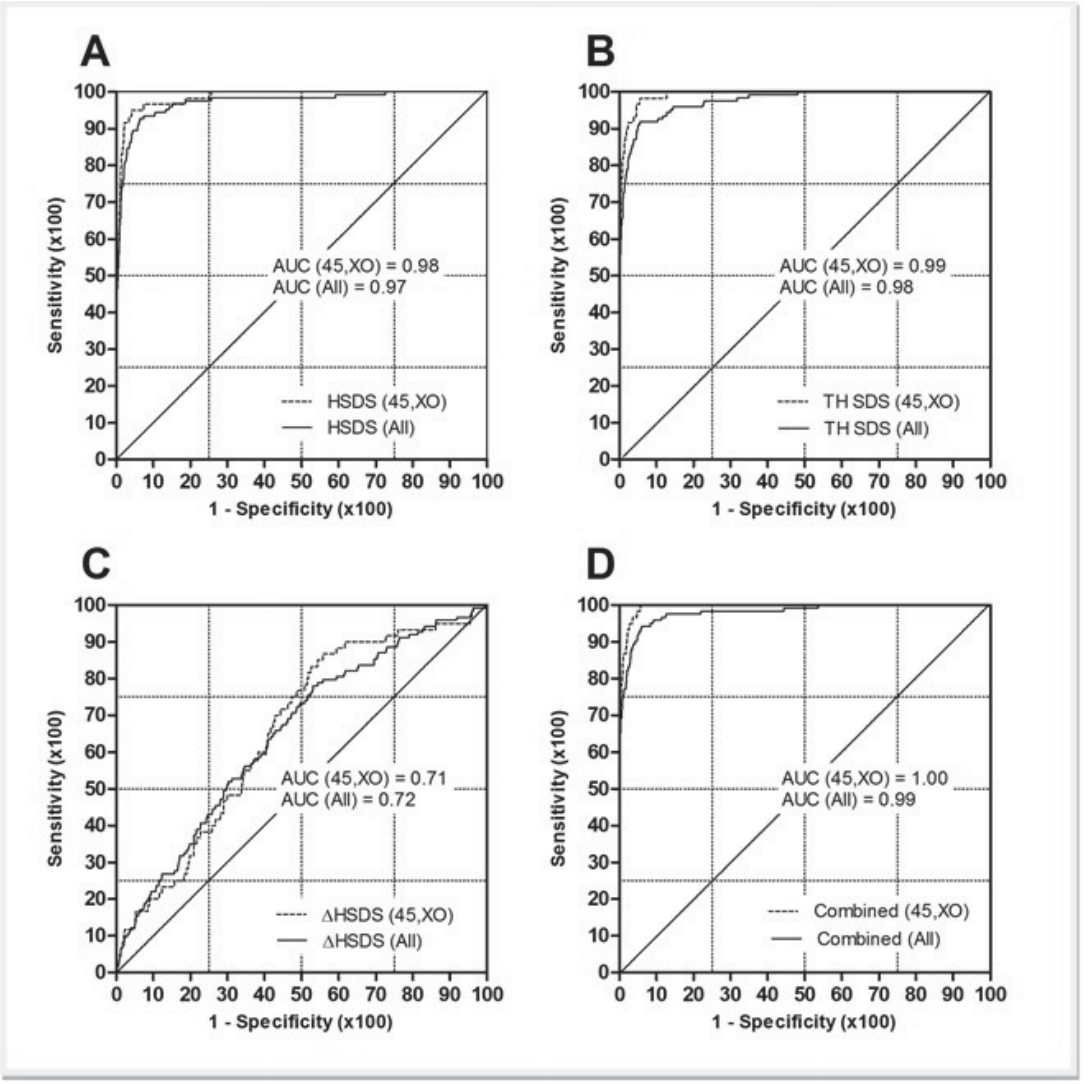

Figure 22. Receiver operating characteristics curves for the three growth screening rules (A–C) and their combination (D) in the TS population (n = 124, solid lines) and in a subsample of TS girls with karyotype 45,XO (n = 60, dashed lines): A, absolute HSDS rule; B, TH SDS rule; C, ΔHSDS rule; D, combination of these three rules (HSDS, TH SDS, or ΔHSDS) (D). Area under ROC-curve is shown separately for every rule.

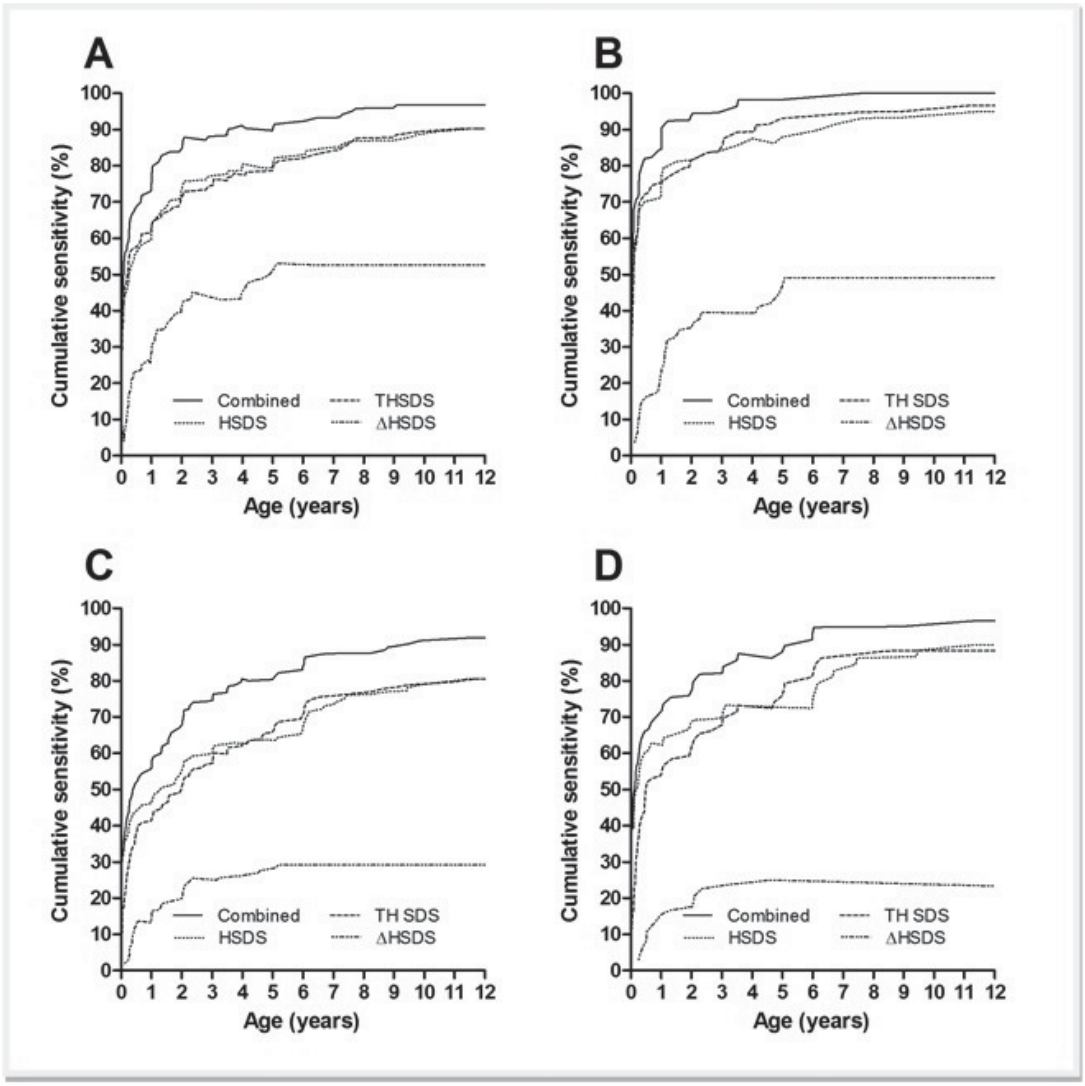

Figure 23. Cumulative sensitivities of four growth screening rules from 0–12 years: HSDS rule, TH SDS, ΔHSDS, and combination of these three in the whole Turner syndrome (TS) group (A and B) (n = 124) and in the subsample of TS girls with karyotype 45,XO (C and D) (n = 60) at specificity levels of 97 and 99%, respectively.

To some extent, all three screening rules complemented each other, as some of the girls were detected by a single rule only. The first alert was triggered by the HSDS rule in 20%, by the TH SDS rule in 24%, and by the ΔHSDS rule in 14% of the TS girls, respectively. Two or three rules were triggered in 42% of TS girls at the same time. In other words, removing any of the three rules from the combination resulted in lower sensitivity than could be achieved by the combination of the three rules. However, the ΔHSDS rule did not improve the screening performance as much as the HSDS and TH SDS rules alone.

Cumulative sensitivities of the HSDS, TH SDS rules and the combination of the three rules increased until 12 years of age, whereas with the ΔHSDS rule, the highest sensitivity was obtained already by the age of 5 years.

5.3.2 Celiac disease

Screening for abnormal growth in CD patients with any single screening parameter resulted in only poor to moderate accuracy (Figure 24). The single best screening parameter was ΔHSDS in girls (AUC = 0.71; 95% CI 0.67 – 0.77) and ΔBMI SDS in boys (AUC = 0.72; 0.64 – 0.80). AUCs for HSDS, BMI SDS and TH SDS varied between 0.60 to 0.68 in girls and 0.64 to 0.67 in boys, respectively. The five screening parameters when combined together (the combination rule, i.e. one or more abnormal screening parameters in a child) performed better than any of the parameters alone. AUC for the combination rule was 0.88 (CI 0.84–0.93) in girls and 0.84 (CI 0.77–0.91) in boys.

The accuracy of each of the growth screening parameters separately and the combination rule for detecting abnormal growth 5 years prior to the diagnosis of CD at 90, 95, and 99% specificity levels are presented in Table 10. Altogether, the sensitivity of the combination rule was 69% for girls and 61% for boys at 90% specificity. The corresponding sensitivities were 49% and 51% with 95% specificity for girls and boys, and 26% for both sexes with 99% specificity, respectively. With the respect to the separate growth screening parameters, the best results were obtained with HSDS and the distance from TH (TH SDS) for girls and BMI SDS for boys.

In the analysis of the growth data of the 5 years before the CD diagnosis, the cumulative prevalence of an abnormal screening result using the combination rule increased the as one came closer to the diagnosis of CD (Figure 25). If the specificity level of the growth screening was set at 90% (i.e. 10% of children with abnormal screening result would not have CD), cumulative percentage of children with abnormal growth prior to or at CD diagnosis was 82% and 70% for girls and boys, respectively. The corresponding percentages at specificity levels 95% and 99% were 66% and 39% in girls, and 65% and 39% in boys. Abnormal growth was seen already two years prior to the CD diagnosis in 57% of the girls and in 48% of the boys (at the specificity level of 90%). The median delay between the first abnormal result by any of the growth screening rules and the CD diagnosis was 3.2 years in girls, and 2.7 years in boys at specificity level of 90%. If the specificity of the screening was set at 95 or 99%, the median delay was 3.0 or 2.6 years in girls, and 2.3 and 2.2 years in boys, respectively.

Table 10. Sensitivity of each of the growth screening parameter and the combination rule in detecting abnormal growth in 177 celiac disease patients (106 girls, 71 boys) 5 years prior to diagnosis at 90, 95, and 99% specificity levels.

	Specificity 90%		Specificity 95%		Specificity 99%	
Screening rule	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**	**Boys**
HSDS	31 (23-41)	25 (16-37)	24 (16-33)	15 (8-26)	10 (5-17)	6 (2-14)
THSDS	31 (20-43)	26 (15-41)	23 (14-35)	16 (7-30)	11 (4-21)	2 (0-11)
BMISDS	23 (15-32)	22 (13-35)	14 (8-23)	15 (8-26)	7 (3-14)	5 (1-13)
ΔHSDS	31 (22-41)	27 (17-40)	20)13-29)	17 (9-29)	10 (5-18)	8 (3-18)
ΔBMISDS	24 (16-35)	41 (28-56)	13 (7-22)	24 (13-38)	7 (2-14)	10 (3-22)
Combination	69 (56-80)	61 (45-77)	49 (36-62)	51 (35-68)	26 (16-39)	26 (13-42)

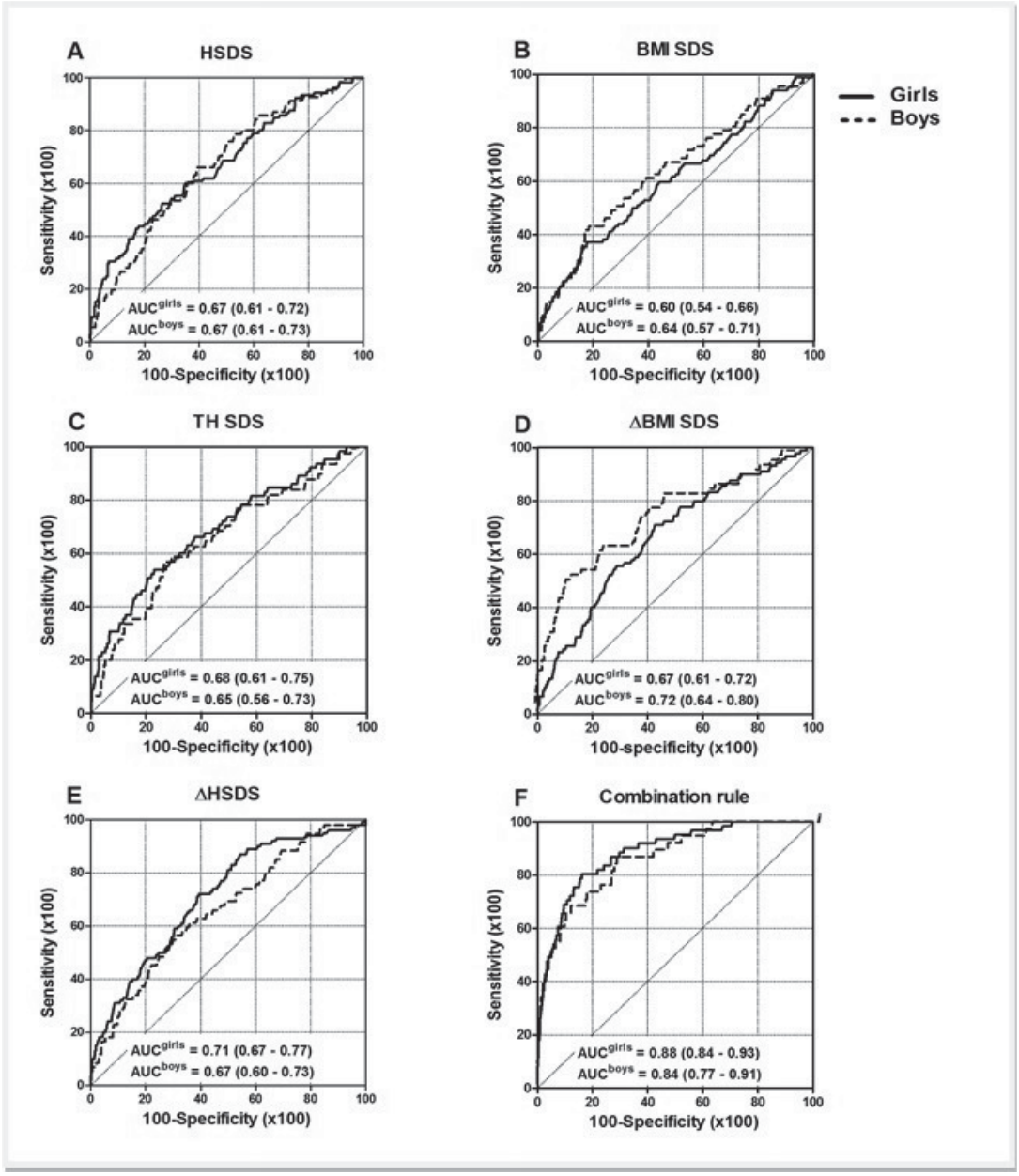

Figure 24. Receiver Operating Characteristic (ROC) curves for the performance of five growth screening parameters and their combination in 106 girls (solid lines) and 71 boys (dashed lines) with celiac disease: Height and body mass index standard deviation score distance from the population mean (HSDS and BMI SDS parameters; panels A and B), HSDS distance from target height (TH SDS) panel C), change in BMI SDS and HSDS over time (ΔBMI SDS and ΔHSDS parameters; panels D and E), and the combination of these five parameters panel F). The area under the curves (AUC) with 95% confidence intervals are shown.

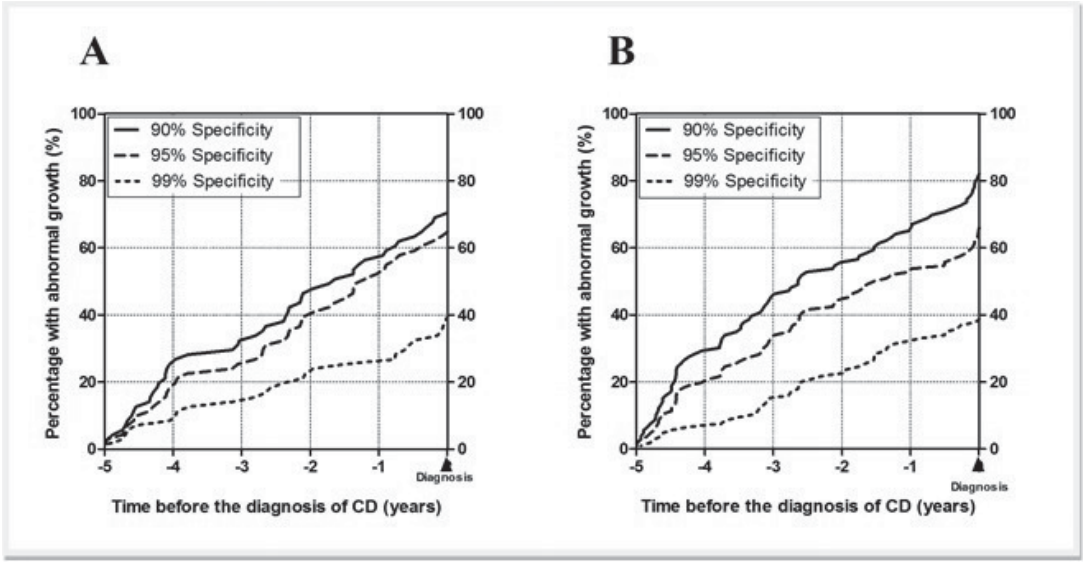

Figure 25. Cumulative percentage of children with abnormal growth five years prior to the diagnosis of celiac disease. Abnormal growth is defined by "an alert triggered by any of the five growth screening parameters", i.e. their use in combination, and specificity levels of 90%, 95%, and 99% in 106 girls (A) and 71 boys (B) are shown. Growth screening parameters are detailed in the text.

5.4 AUTOMATED GROWTH MONITORING PROGRAM

During the AM intervention year, 209 of 32,404 (0.64%) measured children were referred to secondary care for a suspected growth disorder. This was significantly more than in the previous control year, when only 68 of 32,718 (0.21%) measured children were referred onwards (RR for referral 3.10, 95% CI 2.36 to 4.08) (Figure 26).

In the control year, 8 of the 68 referred children (11.8%) were diagnosed with a growth disorder: 4 had a primary or secondary growth disorder (detailed in Figure 26) and 4 had a diagnosis of ISS (after exclusion of other causes of short stature). The number of new diagnoses was significantly higher during the AM intervention year: altogether 48 children of the referred 209 children (23.0%) were diagnosed either with a primary or secondary growth disorder (n = 29) or ISS (n = 19) (detailed in Figure 26). RR for diagnosis of a primary or secondary growth disorder in the AM year was 7.57 (2.57 to 20.82) and if ISS was included, 6.06 (2.87 to 12.80). Alternatively, the RR for being healthy and being referred for a suspected abnormal growth during the AM year was 0.87 (0.78 to 0.98) in comparison to the control year. The diagnostic yield was one growth disorder for every 4090 measurements during the control year, and in one growth disorder for every 675 measurements during the AM intervention year.

All eight children diagnosed with a growth disorder during the control year, and 42 of 48 children (87.5%) during the AM intervention year had an abnormal growth screening result at referral (p = n.s., Fisher's exact test). Twenty-four of the 48 (50.0%) children diagnosed with a growth disorder during the AM year had had abnormal growth screening before the AM intervention year as assessed with standard monitoring, but these children were not referred to secondary care, which resulted in a delay in the diagnosis (Table 11). The median delay was 1.97 years (range 0.08 to 10.26 years).

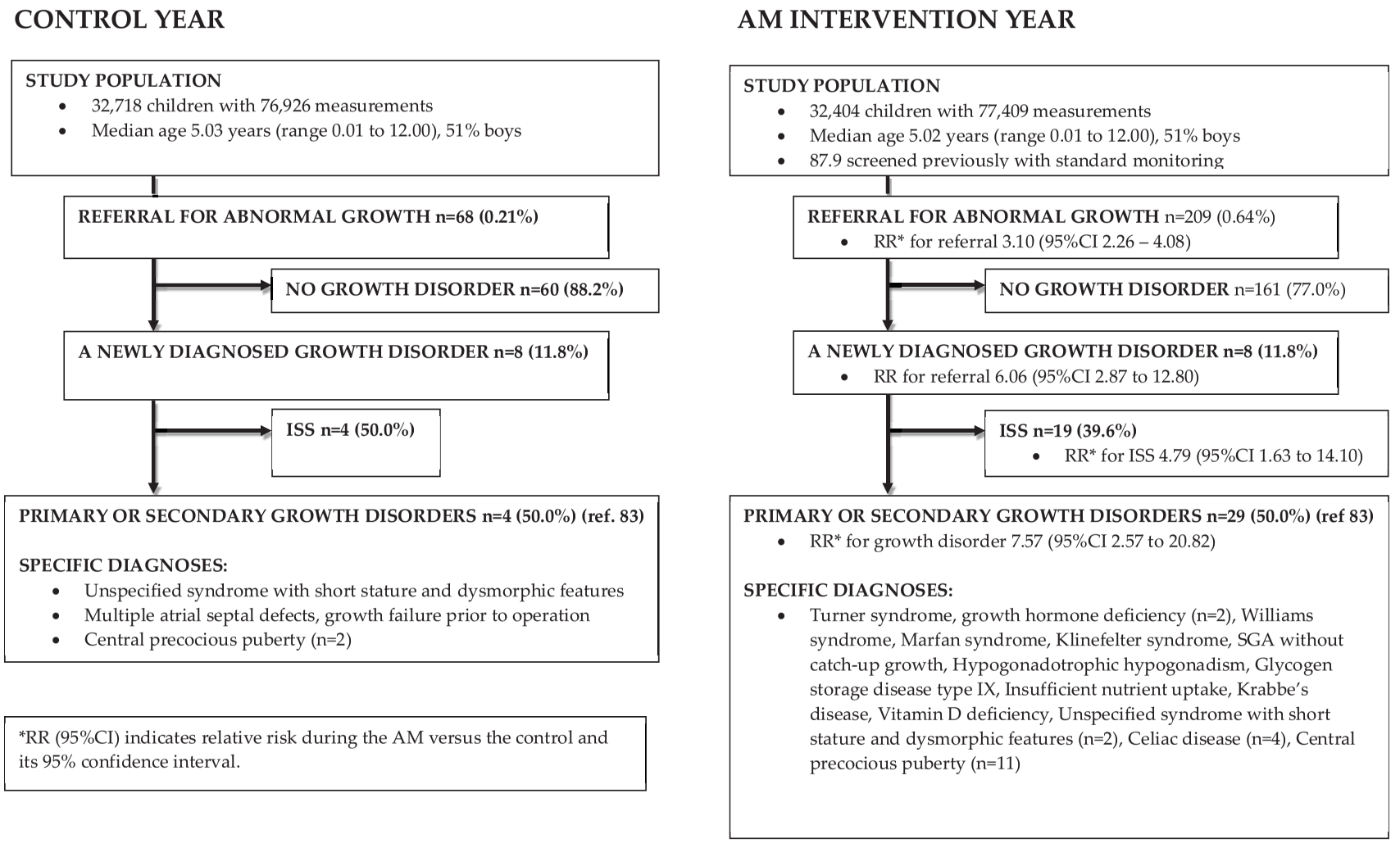

Figure 26. Clinical effectiveness of automated growth monitoring (AM) integrated in an electronic health record in comparison to standard growth monitoring.

Table 11. Diagnostic delay revealed by automated growth monitoring (AM) strategy in 24 of 48 of the newly diagnosed growth disorders.

Diagnose	Delay[a] in diagnosis, years	Age at referral during AM, years	Total number of measurements	Number of abnormal measurements before AM
Syndrome associated with short stature	0.08	0.50	8	1
Idiopathic short stature I	0.17	0.36	6	2
Idiopathic short stature II	0.30	0.72	13	3
Vitamin D deficiency	0.32	3.42	19	1
Williams syndrome	0.41	0.77	11	6
Glycogen storage disease type IX	0.54	1.81	8	2
Idiopathic short stature III	0.85	1.12	13	5
Central precocious puberty I	0.88	9.82	7	1
Central precocious puberty II	0.93	11.40	16	1
Idiopathic short stature IV	0.97	3.01	12	2
Central precocious puberty III	1.13	10.20	7	1
Hypogonadotrophic hypogonadism	1.79	10.57	4	1
Central precocious puberty IV	2.15	10.20	8	2
Idiopathic short stature V	2.81	3.14	18	4
Central precocious puberty V	2.91	7.92	10	3
Turner syndrome	3.01	4.06	14	3
Idiopathic short stature VI	3.13	3.54	15	8
Idiopathic short stature VII	4.05	4.50	22	4
Growth hormone deficiency I	4.54	8.14	12	7
Celiac disease	5.05	8.59	6	3
Idiopathic short stature VIII	5.51	5.56	20	14
Growth hormone deficiency II	7.71	11.77	9	4
Idiopathic short stature IX	8.49	8.93	15	2
Marfan syndrome	10.26	10.27	13	10
Summary, median (range)	**1.97 (0.08 to 10.26)**	**5.03 (0.36 to 11.77)**	**12 (4 to 22)**	**3 (1 to 14)**

[a]The delay was defined as the time from the first abnormal growth screening result to the referral during AM intervention year.

6 Discussion

6.1 GROWTH REFERENCES

New length/height-for-age, weight-for-length/height, and BMI-for-age growth curves were developed to assess the growth of children in Finland. The advantages of these curves are that they include a large, contemporary population-based sample of healthy subjects; there was careful and prospective screenings and exclusion of subjects with potentially faltering growth; up-to-date statistical methods in curve construction; correction of a substantial secular change in the stature of Finnish children; and validation of the constructed BMI-for-age curves against the international standard. It was found that misclassification of the height of contemporary Finnish children is common when using the previous height reference based on subjects born between 1959 and 1971 which further supported the need for an updated growth reference. These curves applicable across the population should be immediately implemented to monitor the growth of children and adolescents in Finland.

The Finnish social security and primary healthcare systems provide free, regular check-ups performed by well-trained nurses with standardized methods during the growth period (144). These visits are available to all permanent residents of Finland regardless of social status or income level; therefore, virtually every child is included. As a result, it is possible to perform population-based growth studies in a primary healthcare setting, such as the present one. Genetically, the inhabitants of the city of Espoo mirror that of the whole of Finland. The population of this city has grown by 10-fold over the past 60 years due to net migration from other parts of the country (152). The proportion of immigrants in Espoo was slightly higher than in the whole of Finland (7% vs. 4%); however, this proportion is continuously changing in other parts of the country as well.

The initial database included the growth data of the entire child population, however, a series of exclusions were made to construct height curves that reflected optimal, healthy linear growth. Cleaning procedures followed the widely accepted methods described for example by the authors of the WHO growth standard study (20,156). Therefore, careful database cleaning was conducted to remove factors possibly influencing linear growth such as prematurity, low birth weight, childhood underweight, and obesity. Furthermore, special attention was paid to excluding children with any disorder or medication considered to possibly affect linear growth. Subsequently, the past and present growth data of each subject visiting either a child health clinic or school health care during the period of one year was assessed systematically according to a specific set of growth screening rules (3,4). Violation of the screening rules resulted in a visual inspection by a pediatric endocrinologist. As a result of these processes, it is believed that the length/height-for-age curves are an estimate of optimal growth.

Optimal weight gain for children and adolescents is much more difficult to define than optimal linear growth. Weight gain is dependent on age and even more strongly on an increase in height, but only very poor or very excessive weight gain is associated with morbidity. Therefore, the original dataset for weight-for-length/height and BMI-for-age references was not cleaned as extensively. Only children with chronic diseases and medications affecting growth were excluded.

For curve construction, the GAMLSS method was chosen; this is the same method recommended for mixed cross-sectional and longitudinal data by the WHO Multicentre Growth Study Group (156).

It was found that secular changes in linear growth exhibited age- and sex-specific features. The growth in length of the height reference 1983–2008 population was more rapid in infants from birth to 5 months of age as compared to the reference 1959–71

population. The difference in height was up to 0.5 (girls) and 0.6 (boys) SDS between the reference 1983–2008 and reference 1959–71 populations by the age of 1 month. The change in infant feeding regimen may explain this difference. Currently, about 60% of infants are breastfed for at least for 6 months (157), whereas breastfeeding was relatively uncommon (5% for 6 months) for infants in the reference 1959–71 population (158). It is known that predominantly breastfed infants grow faster than formula-fed infants during their first months of life. Prolonged exclusive breastfeeding will, however, attenuate linear growth after three months of age (159). Indeed, infants in the reference 1983–2008 population grew at a much lower rate than infants in the reference 1959–71 population between the ages of 3 and 6 months. Some of the differences in height in infancy may also be due to the different statistical methods used in the construction of the two reference periods.

From about the age of 1 year up to 11.5 years in girls and 13 years in boys, there was a steady increase in mean height of the children in the reference 1983–2008 population as compared to the reference 1959–71 population. Boys of the new growth reference were on average up to 5.6 cm (0.70 SDS) taller than in the old reference between the ages of 12 and 13 years. At all ages, secular increases in height were more marked in boys than in girls. In Finland, overweight is currently much more common in boys than in girls (112,113), suggesting that excessive energy gain is one factor resulting in the increased growth rate of boys.

Data on pubertal stages were not included in this sample, but secular increases in height appeared to be linked to earlier maturation and earlier timing of the pubertal growth spurt compared to the reference 1959–71 population as evidenced by the greater increase in height during childhood than during adulthood. An earlier timing of puberty and has been recently described in Danish girls and boys (70,160). In Danish children, the early puberty was associated with higher BMI before the onset of puberty (70,160); however, there was a downward trend in the age at which puberty was attained in both girls and boys, regardless of the BMI, that suggests that the obesity epidemic is not solely responsible for the trend.

Recent growth studies have claimed that the secular increases in adult height are gradually leveling off in several Northern European countries (10). In Finnish children, however, a marked increase was observed in adult height of 1.9 cm in girls and 1.8 cm in boys. The general belief is that the secular increase in height continues until the genetic potential of the population is reached. However, the current knowledge of the genetics of stature is insufficient to make an estimation of height potential of a population.

Growth curves are used for screening of growth-related disorders, and a secular trend in linear growth has a direct influence on this process. One important fact of this study was the demonstration of how outdated cut-off-points could lead to a misclassification of children. Theoretically, an uncorrected secular trend of +0.4 SDS in mean height without a change in SD for height would mean that only 0.8% of children remained below the lower -2 SDS limit and as many as 5.5% were above the upper +2 SDS limit, instead of the expected 2.3% at both ends. These observations were consistent with such a rate of misclassification by the mean ±2 SD limits. Incorrect cut-off points at ±2 SD by 0.4 SDS would results in a 3.4% reduction in specificity and up to a 32.6% reduction in sensitivity of screening of short and tall stature, which is unacceptable.

Monitoring of weight is important in the detection of nutritional changes such as risk of malnutrition or obesity, or of chronic diseases affecting weight. Weight reference curves should include the definition of a normal weight range between thinness and overweight. In adults, one can use BMI cut-off points that have been agreed upon internationally: underweight BMI is <18.5 kg/m2); normal weight BMI is 18.5–24.9 kg/m2; overweight BMI is 25.0–29.9 kg/m2; and obesity BMI is >30 kg/m2 (135). It is important to remember that in children, body composition varies at according to age; therefore, factors affecting weight include not only height and sex, but also, to some extent, age of the child. Furthermore,

body composition and build also differ between populations (119). Thus, BMI reference curves need to be adjusted at least for sex and age and possibly, also for ethnicity.

Initially, BMI-for-age percentile curves were constructed for children older than 2 years. Then, by using a widespread method devised by Cole, which uses BMI-for-age percentiles passing through various adult BMI cut-offs, it was possible to calculate BMI percentiles to define various grade of thinness, overweight, and obesity for Finnish children (135,136).

The prevalence of grade 1 thinness (percentile passing through a BMI of 18.5 at the age of 18 years) in the present sample was as high as 12.1% for girls and 17.9% for boys. As it would be both impractical and confusing to define such a high number of children and adolescents having grade 1 thinness, one can recommend using only grade 2 and grade 3 thinness percentile curves (passing through BMIs of 17 and 16 at the age of 18 years, respectively).

For Finnish boys, the prevalence of obesity was approximately the same as that recently reported by Vuorela et al. (4.4 % vs. 3.2%), but for girls, the prevalence was about half in the present sample (1.8% vs. 4.7%) (113). These results are not directly comparable, however, because here used BMI percentiles specific for Finnish children were used while the IOTF cut-offs were used in the other study.

In comparison to weight-for-length/height, BMI-for-age has the advantage of being able to capture the changes in the weight-length/height relation with age and thus it is a measure that can be used continuously up to adulthood, as well as compared internationally. However, due to significant changes in BMI-for-age during the age of 0 to 2 years, i.e. first the rapid increase and then the reduction; it is still recommended to use weight-for-length/height in that age group instead of BMI-for-age. The use of weight-for-length/height has been criticized for several reasons. As reported by Cole (161), it is not independent on age, and therefore, it should be used only over a narrow age range. Furthermore, there are no cut-off values using weight-for-length/height to define underweight and obesity. Therefore, for older children the use of BMI-for-age rather than weight-for-length/height seems generally to be more advisable. For the screening of obesity in children and adolescents, the United States Preventive Services Task Force recommends the use of BMI-for-age beginning at 6 years of age (162).

The new Finnish growth references for length/height-for-age, weight-for-length/height and BMI-for-age created in this study using a contemporary, large Finnish population-based sample are now available for primary healthcare providers and clinicians for updated growth monitoring. There are several advantages in replacing the growth curves currently in use by these updated and new references. The use of these new references should result in fewer misclassifications of normal growth in children thereby preventing unnecessary examinations in children with suspected growth failure.

6.2 NATIONAL VERSUS MULTI-ETHNIC GROWTH REFERENCES

AH varies significantly among populations, and is strongly genetically determined with heritability estimates of around 80% (80). Therefore, the childhood linear growth patterns are probably not as strongly determined as the weight by the optimal nutritional, environmental and psychosocial factors. In this respect the original assumption of uniform growth among populations may be incorrect and even affect adversely the screening of growth disorders.

Height assessment in children growing at the outer percentiles with potential morbidity may be flawed if one uses the WHO standards. This thesis is, thought to be, the first to report the suboptimal accuracy of screening of a height disorder with the WHO standard in comparison to a population specific reference. Furthermore, Finnish children are on average 0.2-0.8 SDS taller than the WHO standard's (I,20). In a recent study from Norway and Belgium, the proportions of the healthy children outside the ±2 SDS of WHO standards were different than expected (15). Thus the concept of "similarity" of heights among

children from different ethnic backgrounds under optimal conditions is questionable due to the fact that genetic differences have an impact on linear growth.

Further studies in other populations and with other growth disorders are warranted. Before implementing the WHO growth charts in height screening, their performance should ideally be tested in the population for whom they are intended for.

6.3 GROWTH MONITORING CUT-OFF VALUES FOR ABNORMAL GROWTH

Growth monitoring is a fundamental part of primary healthcare in children, but the performance of various growth monitoring parameters in the context of screening program has remained inadequately explored. A recent systematic review on growth monitoring for short stature claimed that optimal cut-off points for abnormal growth are virtually absent (1). One major strength of the present study was the establishment of population-based screening cut-off values for abnormal growth, which were developed using a large, contemporary height data set of healthy children.

This study represented an extensive methodological exercise to optimize auxological screening of abnormal growth. First, age-specific normal values were calculated for the height distance from TH. The data showed that height distance from TH in a population was age-dependent and should be taken into account in growth monitoring. Second, a method was developed based on the change in height SDS and BMI SDS to assess changes in growth rate over time between age points from 0 to 12 years. As far as is known, this is the first study to define population-based, age-specific reference values for height SDS distance from the TH SDS, as well as limits for the changes in growth rate that are scalable freely between any two age points. Ultimately, these new population-based auxological screening cut-off values were validated for height SDS, BMI SDS, height distance from TH SDS and changes in growth rate (height SDS and BMI SDS) in a retrospective clinical datasets of 124 girls with TS, and 106 girls and 71 boys with CD, respectively.

6.4 AUXOLOGICAL SCREENING ACCURACY FOR TURNER SYNDROME

In this study TS was used as a model disorder because of the fact that short stature is often the only or at least the most obvious clinical sign. By using three growth monitoring parameters for height (height SDS, TH SDS and ΔHSDS), it was possible to detect abnormal growth in TS with excellent accuracy already at a young age. However, growth monitoring programs aim at identifying not only TS but a variety of other disorders affecting growth. Grote et al. (29) have shown that the growth patterns of the most prevalent growth disorders (TS, GHD, CD and cystic fibrosis) vary by age and the screening rule to be used, but overall TS appears to be an optimal target group for screening. However, further studies in clinical disorders other than TS are still warranted.

An ideal growth monitoring program should have a high sensitivity in order to detect as many abnormally growing children as possible, with the kind of specificity that does not produce too many unnecessary referrals. However, one always has to make a trade-off between sensitivity and specificity. For the height SDS cut-off (or height percentile cut-off) values, the specificity is pre-defined by the growth references without any knowledge of the sensitivity for each of the detectable growth disorders. In the previous study of van Buuren et al. (28) 70% of TS girls could be detected with the HSDS rule with a specificity of 93%. In contrast, in this study it was possible to detect as many as 93% of TS girls with the same specificity by using the HSDS rule. The difference can be explained by two factors. The TS girls in the present cohort were born between 1978 and 2009, as were the majority of the children in the reference population (I) whereas in the Dutch study, TS girls were older than children in the reference data (born between 1968 and 1996 in comparison to reference girls born between 1989 and 1990). Furthermore, the reference children were on average 0.31 SDS shorter than the Dutch reference population (28).

Height distance from TH, in comparison to height SDS, is believed to improve sensitivity without significantly reducing specificity, because the SD for TH is narrower than the SD for height (131). Several methods have been proposed for calculating TH(132-134). The present study, the TH SDS formula of Wright et al (132) was very accurate in predicting the adult height and was also consistent with height SDS in all age ranges in the population sample.

In the study of Van Buuren et al (28), height distance from TH in the screening for TS was assessed as well, although in their study, a large proportion of maternal or paternal heights were imputed due to missing data. Screening of TS with the TH rule in this study produced similar performance as that reported by Van Buuren et al (28). In another Dutch study reported by Grote et al. (29), it was found that the use of TH was superior to height SDS only in growth screening. Therefore, parental heights should be systematically recorded for each child and TH-based screening may then become useful, especially in multi-ethnic populations when population-specific growth references are not available. Gozzi et al. (163) reported that short parents tend to overestimate their height, and therefore actual measurement of parental heights if possible is preferable.

The change in growth rate is virtually an unexplored approach in the screening of growth disorders, and population-based reference values to describe normal changes are virtually non-existent (3,4). One advantage in the method reported in this study is that the cut-off values for abnormal growth rate can be defined for any age range between 0 and 12 years. Nevertheless, the utilization of growth rate (ΔHSDS rule) is highly dependent on the accuracy of height measurements.

It does seem that almost 40% of growth disorders can be identified based on an abnormal growth rate before the child is abnormally short or tall (unpublished observation). In one previous study, the combination of height-for-age, height distance from TH and change in growth rate has been reported to detect children with short stature with good sensitivity and acceptably high specificity (29). The result in the screening of TS substantiates these findings, although TS is a growth disorder with a prenatal origin and thus the main growth feature is a short stature for age or abnormal distance of height from TH. Therefore, screening by using the changes in growth rate is probably more accurate in disorders that typically manifest via a decrease in height SDS or height percentile, e.g. GHD, hypothyroidism and CD.

Growth in TS girls typically is affected already in utero and in infancy, but nonetheless in two previous studies only about one third of TS girls had been identified by mid-childhood (83,84). The present results on cumulative sensitivity by age revealed that TS girls can be potentially detected much earlier, as many as 80% (specificity 99%) by the age of 5 years if one undertakes systematic population-based growth monitoring and by following the screening rules. Furthermore, karyotype should be examined for girls with typical clinical findings for TS (e.g. lymphedema at birth, webbed neck or cubitus valgus), especially if they are short.

6.4 AUXOLOGICAL SCREENING ACCURACY FOR CELIAC DISEASE

This study revealed that the majority of the children diagnosed with CD could have been detected by appropriate auxological screening. Most CD children developed growth failure prior to the diagnosis, and on average, CD children were shorter than the healthy reference population. Thus auxological screening would be a simple and non-invasive method to improve the early diagnosis of CD in children. The best results should be obtained by implementing a well-established longitudinal growth monitoring program, and systematic screening with contemporary cut-off values for both height and weight.

The major strengths of this study was the use of a population-based, contemporary growth reference and cut-off values, including the change in height SDS and BMI SDS over

time, which enable assessment of subtle changes in the growth rate. Only a few previous studies have assessed the use of growth rate in screening (29).

The weakness of this study was its retrospective nature and data collection from patient files, which did not include systematic notes on intestinal and extra-intestinal symptoms prior to the diagnosis of CD. However, it is believed that the retrospective growth data were not biased. Data were retrieved from electric health records, based on population based growth monitoring program which has been operative from the 1990s. All children the present CD cohort had been measured according to this program. The quality of growth data gathered at routine visits has also been assessed; false measurements, typing errors, missing values, or duplicate recordings are scarce (97).

The clinical pattern of childhood CD has changed from the classical triad – failure to thrive, diarrhea and abdominal distention – to a large variety of nonspecific signs and symptoms (85-89), as shown also in the present cohort. Abnormal growth is the most common extra-intestinal symptom of CD (164). The probability of CD is estimated to range from 19 to 59% in children with short stature of a non-endocrinological cause (164-168). Nevertheless, severe growth failure is uncommon in children with CD today, particularly in the developed countries (164-168). Growth failure in contemporary CD children was not even seen in the study of Savilahti et al. (169), which is in contradiction with the present observations. This discrepancy was probably due to the fact that the growth failure is relatively subtle in its nature, and as they used outdated growth references in the evaluation of growth, the secular changes in height introduced a systemic error into their data. The present findings of impaired growth in CD patients are in agreement with the study of Korponay-Szabo et al (170). They performed a universal serological screening for CD among 6 year-old children in one county (n = 2360), and diagnosed altogether 32 new CD cases. These 32 children were on average shorter and lighter than their healthy peers (170).

Consistent with the present results, in Dutch cohort van Dommelen et al. recently showed that a change in BMI SDS was the most accurate parameter to detect CD (171). However, the Dutch cohort was composed almost entirely of infants and small children (0 to 2.5 years of age) whereas the children in the present study ranged in age from infancy to late puberty and therefore the two studies are not directly comparable. It was found that the best screening accuracy for CD was achieved by combining various growth screening parameters. Nevertheless, the screening accuracy for CD still remained inferior to some other disorders affecting growth, such as Turner syndrome (29). The diagnostic accuracy of any screening program is always a trade-off between sensitivity and specificity. Growth monitoring cut-offs are intended to detect as many abnormally growing children as possible (high sensitivity) without producing too many unnecessary referrals or further investigations (high specificity). In that respect, relatively low specificity can be considered as acceptable for CD, because detected children can be investigated further by a simple and cheap serological testing.

Recent data have shown that CD remains severely underdiagnosed in the Western populations (86,90-92), and therefore new tools to improve diagnosis are needed. Universal population screening by serology is not currently advised. Growth monitoring is performed in almost every developed country. Improvements towards systematic growth screening by pre-established rules would facilitate more efficacious screening of disorders such as CD. This was shown also in the present study by a significant diagnostic delay between the first abnormal height or weight measurement and the diagnosis of CD. In addition, the use of population based growth reference instead of universal reference can facilitate the identification of subtle forms of growth failure, as shown previously in the context of Turner syndrome (II). It has been demonstrated here that implementation of a growth monitoring program into EHR and computerization of the screening is a feasible and effective method to improve the early diagnostics of growth disorders (V). Consequently, it was recommended that systematic growth screening is adopted as a primary method for

early detection of chronic disorders affecting growth, such as CD. A prospective population-based study is warranted to evaluate the benefits and costs of such a screening program.

The weakness of the both studies, in girls with TS and in children with CD, was their retrospective nature and the collection of data from patient files. The best approach would be prospective population-based screening study in which growth screening parameters were compared to pre-defined examination in secondary healthcare (e.g. karyotype in girls with short stature) or serological screening tests for CD. However, growth monitoring is not intended to detect only one or two disorders affecting growth, but systematic growth monitoring program can improve the screening process of growth disorders in general (125).

6.5 AUTOMATED GROWTH MONITORING PROGRAM

This population-based cohort study demonstrated that automated growth monitoring implemented in the primary care EHR system can improve the effectiveness of growth screening in children. The AM strategy improved the detection rate of growth disorders by 6-7-fold. It also identified numerous children with a growth disorder who were being previously missed by the standard growth monitoring.

A major strength of this study was the use of a large unselected target population covered by well-organized primary care. The acceptance of the public growth screening during the AM year remained the same as in the control year and was almost 100% of the eligible population(172). In previous growth monitoring studies, the reported percentage of eligible children measured has ranged from 45 to 90% (29,32,137-148) Another strength of the present study was the wide array of growth conditions screened for, including primary and secondary disorders causing either short or tall stature. Only two of the 12 previous studies on growth monitoring programs (32,142) have focused on both short and tall stature, the others have concentrated on short stature only (29,139-141,143-148). The present data revealed that disorders causing excessive growth are also common among stature related disorders and should be included in monitoring strategies. In our study, the benefits of AM might have been exaggerated, because the majority of the child population, nearly 90%, had also been screened in the preceding years using the standard monitoring. For the same reason, the diagnostic yield during the AM does not reflect the total prevalence of growth disorders in the population, but the incremental yield. One limitation of the study was that those assessed as healthy were not followed after the AM intervention. Thus, only false positive cases, and a subset of true positive cases were identified.

This is thought to be the first study to assess the impact of an automated growth monitoring integrated into EHR in primary care. The German program described by Keller et al (32) is another computer-based monitoring system, in which routine height measurements is being gathered in more than 100 participating paediatric practices throughout a wide area of Germany. Children with heights above the 97th percentile or below the 3rd percentile on the German synthetic normal curve were highlighted to the relevant practice, and children were referred for specialist investigation if this was considered necessary. This program clearly produced the best overall diagnostic yield (one per 545) of all of the 12 previously published growth screening programme studies (29,32,139-148). The diagnostic yield in the present study during the AM intervention was close to that found in the Keller study (one per 675) (32). However, based on the prevalence of disorders potentially affecting linear growth, one can assume that even during the AM, a significant amount of pathological growth will remain undiagnosed but they may be detected in subsequent years. The significant amount of non-referrals during the standard monitoring led to delayed diagnoses. Automation of the screening rules during the AM led to recognition of all children with abnormal screening but the present referral rate only increased from 0.2% to 0.6%. This low referral rate can be explained by the online

consultation by a pediatric endocrinologist, as only 13% of the alarmed cases were ultimately referred to specialist care for further investigation. In addition, it reflects the fact that the screening rules are far from optimal, although their performance can be improved by automation. Even though most industrialized countries have growth monitoring programs for children, there is very little evidence-based data to determine the best screening rules for detecting abnormal growth (1,29). This area clearly warrants further studies.

The present data support the idea that growth monitoring is an effective option in general and support the findings of Fayter at al. (137). Early diagnosis is an issue that will hugely affect the benefits of any growth monitoring programme. The issue of late versus early detection could not be fully addressed in the present model, because of the relatively small number of disorders diagnosed. However, it was demonstrated clearly that diagnoses could be made earlier with the AM than with the manually performed standard monitoring.

Healthcare in the developed countries is entering a new era in which healthcare systems will be the key to delivering safe, effective, and efficient care. EHRs will play a central role in this transformation. EHRs can help clinicians to adhere to guideline-based care and reduce medication errors (173,174), but empirical data showing either quality improvement or cost savings from EHR adoption are scarce. This study reveals that the automation of several growth screening steps, using the EHR systems currently available, is a simple way to improve the detection of growth disorders in a general child population. Despite existing differences in growth monitoring programs internationally, it is likely that automation of growth screening will be also beneficial for other populations. It is conceivable that very complex screening algorithms could be incorporated into fully computerized monitoring programs to obtain reliable automated growth screening. However, some important issues, such as the optimum ages for screening and the evidence-based screening criteria still remain unresolved.

7 Conclusions

In conclusion, an optimal growth monitoring program requires standardized equipment, well-trained nurses, an adequate population based reference and evidence-based screening rules and referral criteria approved by pediatric growth specialists.

The new Finnish growth references for length/height-for-age, weight-for-length/height, and BMI-for-age created in this study using a contemporary, large, Finnish population-based sample are now available for primary health care providers and clinicians to permit updated growth monitoring. There are several advantages in replacing the growth curves currently in use with these up-dated references. The adoption of these new references should result in fewer misclassifications of normal growth in children, thereby preventing unnecessary examinations in children with suspected growth failure.

This is the first study to report the suboptimal accuracy of screening of a height disorder with the WHO standard in comparison with a population specific reference. Further studies in other populations and with other growth disorders are warranted. Before implementing the WHO growth charts in height screening, their performance should ideally be tested in the population in whom they are intended to be used.

The establishment of population-based, validated cut-off values for height-for-age, height distance from TH and changes in growth rate would represent a crucial step towards evidence-based growth monitoring, and should be implemented in growth monitoring programs. The screening algorithms such as the cut-off values for growth rate are complex, and therefore their efficient use requires computerization.

The integration of screening algorithms into contemporary electronic patient management systems could be an interesting way to screen for growth disorders in the future. Automation of several growth screening steps, using the EHR systems available, is a simple and cost effective way to improve the detection of growth disorders in a general child population. Despite existing differences in growth monitoring programs internationally, it is predicted that automation of growth screening will also be beneficial for other populations. It is conceivable that very complex screening algorithms could be included in fully computerized monitoring programs to help obtain reliable automated growth screening. However, some important issues, such as the optimum ages for screening and the evidence-based screening criteria still remain unresolved.

8 References

(1) Craig D, Fayter D, Stirk L, Crott R. Growth monitoring for short stature: update of a systematic review and economic model. Health Technol Assess 2011; 15:iii-iv, 1-64.

(2) Sorva R, Perheentupa J, Tolppanen EM. A novel format for a growth chart. Acta Paediatr Scand 1984; 73:527-529.

(3) Sorva R, Tolppanen EM, Perheentupa J. Variation of growth in length and weight of children. I. Years 1 and 2. Acta Paediatr Scand 1990; 79:490-497.

(4) Sorva R, Lankinen S, Tolppanen EM, Perheentupa J. Variation of growth in height and weight of children. II. After infancy. Acta Paediatr Scand 1990; 79:498-506.

(5) Cole TJ. Secular trends in growth. Proc Nutr Soc 2000; 59:317-324.

(6) Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, et al. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000; 47:316-323.

(7) Wikland KA, Luo ZC, Niklasson A, Karlberg J. Swedish population-based longitudinal reference values from birth to 18 years of age for height, weight and head circumference. Acta Paediatr 2002; 91:739-754.

(8) Juliusson PB, Roelants M, Eide GE, Moster D, Juul A, Hauspie R, et al. Growth references for Norwegian children. Tidsskr Nor Laegeforen 2009; 129:281-286.

(9) Tanner JM. Growth as a measure of the nutritional and hygienic status of a population. Horm Res 1992; 38 Suppl 1:106-115.

(10) Larnkaer A, Attrup Schroder S, Schmidt IM, Horby Jorgensen M, Fleischer Michaelsen K. Secular change in adult stature has come to a halt in northern Europe and Italy. Acta Paediatr 2006; 95:754-755.

(11) Gudbjartsson DF, Walters GB, Thorleifsson G, Stefansson H, Halldorsson BV, Zusmanovich P, et al. Many sequence variants affecting diversity of adult human height. Nat Genet 2008; 40:609-615.

(12) Weedon MN, Lettre G, Freathy RM, Lindgren CM, Voight BF, Perry JR, et al. A common variant of HMGA2 is associated with adult and childhood height in the general population. Nat Genet 2007; 39:1245-1250.

(13) Weedon MN, Lango H, Lindgren CM, Wallace C, Evans DM, Mangino M, et al. Genome-wide association analysis identifies 20 loci that influence adult height. Nat Genet 2008; 40:575-583.

(14) Lettre G, Jackson AU, Gieger C, Schumacher FR, Berndt SI, Sanna S, et al. Identification of ten loci associated with height highlights new biological pathways in human growth. Nat Genet 2008; 40:584-591.

(15) Juliusson PB, Roelants M, Hoppenbrouwers K, Hauspie R, Bjerknes R. Growth of Belgian and Norwegian children compared to the WHO growth standards: prevalence below -2 and above +2 SD and the effect of breastfeeding. Arch Dis Child 2011; 96:916-921.

(16) Binns C, Lee M. Will the new WHO growth references do more harm than good? Lancet 2006; 368:1868-1869.

(17) Bonthuis M, van Stralen KJ, Verrina E, Edefonti A, Molchanova EA, Hokken-Koelega AC, et al. Use of national and international growth charts for studying height in European children: development of up-to-date European height-for-age charts. PLoS One 2012; 7:e42506.

(18) Hui LL, Schooling CM, Cowling BJ, Leung SS, Lam TH, Leung GM. Are universal standards for optimal infant growth appropriate? Evidence from a Hong Kong Chinese birth cohort. Arch Dis Child 2008; 93:561-565.

(19) Ziegler EE, Nelson SE. The WHO growth standards: strengths and limitations. Curr Opin Clin Nutr Metab Care 2012; 15:298-302.

(20) WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. Acta Paediatr Suppl 2006; 450:76-85.

(21) Wright C, Lakshman R, Emmett P, Ong KK. Implications of adopting the WHO 2006 Child Growth Standard in the UK: two prospective cohort studies. Arch Dis Child 2008; 93:566-569.

(22) van Buuren S, van Wouwe JP. WHO Child Growth Standards in action. Arch Dis Child 2008; 93:549-551.

(23) Himes JH editor. Anthropometric assessment of nutritional status. New York: Wiley-Liss; 1991.

(24) Pietrobelli A, Faith MS, Allison DB, Gallagher D, Chiumello G, Heymsfield SB. Body mass index as a measure of adiposity among children and adolescents: a validation study. J Pediatr 1998; 132:204-210.

(25) Prospective Studies Collaboration, Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 2009; 373:1083-1096.

(26) Garner P, Panpanich R, Logan S. Is routine growth monitoring effective? A systematic review of trials. Arch Dis Child 2000; 82:197-201.

(27) Scherdel P, Salaun JF, Robberecht-Riquet MN, Reali L, Pall G, Jager-Roman E, et al. Growth monitoring: a survey of current practices of primary care paediatricians in europe. PLoS One 2013; 8:e70871.

(28) van Buuren S, van Dommelen P, Zandwijken GR, Grote FK, Wit JM, Verkerk PH. Towards evidence based referral criteria for growth monitoring. Arch Dis Child 2004; 89:336-341.

(29) Grote FK, van Dommelen P, Oostdijk W, de Muinck Keizer-Schrama SM, Verkerk PH, Wit JM, et al. Developing evidence-based guidelines for referral for short stature. Arch Dis Child 2008; 93:212-217.

(30) Hall DM. Growth monitoring. Arch Dis Child 2000; 82:10-15.

(31) Kiess W, Gausche R, Keller A, Burmeister J, Willgerodt H, Keller E. Computer-guided, population-based screening system for growth disorders (CrescNet) and on-line generation of normative data for growth and development. Horm Res 2001;56 Suppl 1:59-66.

(32) Keller E, Gausche R, Meigen C, Keller A, Burmeister J, Kiess W. Auxological computer based network for early detection of disorders of growth and weight attainment. J Pediatr Endocrinol Metab 2002; 15:149-156.

(33) Tanner JM editor. A history of the study of human growth. London: Cambridge University Press; 1981.

(34) Tanner JM. Some notes on the reporting of growth data. Hum Biol 1951; 23:93-159.

(35) C. F. Jambert. De causis incrementum corporis animalis liminantes. Halle: Fürstenia: ; 1754.

(36) Buffon, C. L. L. de. Histoire Naturelle, Generale et Particuliere. Paris: L'Imprimerie Royale; 1777.

(37) Scammon RE. The first seriatim study on human growth. Am J Phys Anthropol 1927; 10:329.

(38) Thompson DW. On Growth and Forms. 2nd ed. New York : Macmillan: Cambridge: University Press; 1942.

(39) Quetelet A editor. Letters Adreessed to HRH the Grand Duke of Saxe-Coburg and Gotha on the Theory of Probabilities as Applied to the Moral and Political Sciences, trans. Olinthus Gregory Downes. London: Leyton; 1849.

(40) Roberts C. The physichal requirements of factory children. Journal of the Statistical Society 1876; 39:681-733.

(41) Galton F. Anthropometric percentiles. Nature 1885; 31:223-5.

(42) Bowditch HP. The growth of children studied by Galton's percentile grades. In: 22nd Annual Report of the State Board of Health of Massachusetts Boston: Wright and Potter 1891:479-525.

(43) Bowditch HP. The relation between growth and disease. Transactions of the American Medical Association 1881; 32:371-7.

(44) Boas F. The growth of children. Science 1912; 36:815-18.

(45) Robertson TB. Criteria of normality in the growth of children. Medical Journal of Australia 1922(i):570-6.

(46) Dumoutet P. Contribution á l'étude du poids harmonique chez les enfants du deuzième age. Arch med enf 1921; 24:352.

(47) Quatelet A. Anthropomètrie ou mesure des different faculties de l'homme. Anthropomètrie Brussels; 1871.

(48) Bäckström-Järvinen L. Heights and Weights of Finnish Children and Young Adults. Helsinki: Children Hospital, University of Helsinki; 1964.

(49) Westerlund F. Studier i Finlands Anhropologi. - Bulletin de la Société de Geographié de Finlande. Fennia 1900; 2:1.

(50) Wilskman I. Tilastollisia tietoja Suomen koulunuorison ruumiillisesta kehityksestä. Helsinki: Suomalaisen kirjallisuuden seuran kirjapaino osakeyhtiö; 1916.

(51) Söderström H. Helsingin suomenkielisten kansakoululaisten paino ja pituus (Weight and Height of Pupils in the Finnish-language Elementary Scholls in Helsinki; in Finnish). Duodecim 1926; 42:971.

(52) Karlberg J. On the construction of the infancy-childhood-puberty growth standard. Acta Paediatr Scand Suppl 1989; 356:26-37.

(53) Karlberg J. On the modelling of human growth. Stat Med 1987 Mar;6(2):185-192.

(54) Karlberg J, Engstrom I, Karlberg P, Fryer JG. Analysis of linear growth using a mathematical model. I. From birth to three years. Acta Paediatr Scand 1987; 76:478-488.

(55) Karlberg J, Fryer JG, Engstrom I, Karlberg P. Analysis of linear growth using a mathematical model. II. From 3 to 21 years of age. Acta Paediatr Scand Suppl 1987; 337:12-29.

(56) Magnus P. Distinguishing fetal and maternal genetic effects on variation in birth weight. Acta Genet Med Gemellol (Roma) 1984; 33:481-486.

(57) Magnus P. Further evidence for a significant effect of fetal genes on variation in birth weight. Clin Genet 1984; 26:289-296.

(58) Schwarzler P, Bland JM, Holden D, Campbell S, Ville Y. Sex-specific antenatal reference growth charts for uncomplicated singleton pregnancies at 15-40 weeks of gestation. Ultrasound Obstet Gynecol 2004; 23:23-29.

(59) Gafni RI, Weise M, Robrecht DT, Meyers JL, Barnes KM, De-Levi S, et al. Catch-up growth is associated with delayed senescence of the growth plate in rabbits. Pediatr Res 2001; 50:618-623.

(60) Emons JA, Boersma B, Baron J, Wit JM. Catch-up growth: testing the hypothesis of delayed growth plate senescence in humans. J Pediatr 2005; 147:843-846.

(61) Karlberg J. The infancy-childhood growth spurt. Acta Paediatr Scand Suppl 1990; 367:111-118.

(62) Liu Y, Albertsson-Wikland K, Karlberg J. Long-term consequences of early linear growth retardation (stunting) in Swedish children. Pediatr Res 2000; 47:475-480.

(63) Hochberg Z, Albertsson-Wikland K. Evo-devo of infantile and childhood growth. Pediatr Res 2008; 64:2-7.

(64) Albertsson-Wikland K, Kristrom B, Jonsson B, Hochberg Z. Long-term response to GH therapy in short children with a delayed infancy-childhood transition (DICT). Pediatr Res 2011; 69:504-510.

(65) Miura M, Tanaka K, Komatsu Y, Suda M, Yasoda A, Sakuma Y, et al. Thyroid hormones promote chondrocyte differentiation in mouse ATDC5 cells and stimulate endochondral ossification in fetal mouse tibias through iodothyronine deiodinases in the growth plate. J Bone Miner Res 2002; 17:443-454.

(66) Kindblom JM, Gothe S, Forrest D, Tornell J, Tornell J, Vennstrom B, et al. GH substitution reverses the growth phenotype but not the defective ossification in thyroid hormone receptor alpha 1-/-beta-/- mice. J Endocrinol 2001; 171:15-22.

(67) Stevens DA, Hasserjian RP, Robson H, Siebler T, Shalet SM, Williams GR. Thyroid hormones regulate hypertrophic chondrocyte differentiation and expression of parathyroid hormone-related peptide and its receptor during endochondral bone formation. J Bone Miner Res 2000; 15:2431-2442.

(68) Parker CR,Jr. Dehydroepiandrosterone and dehydroepiandrosterone sulfate production in the human adrenal during development and aging. Steroids 1999; 64:640-647.

(69) Voutilainen R, Perheentupa J, Apter D. Benign premature adrenarche: clinical features and serum steroid levels. Acta Paediatr Scand 1983; 72:707-711.

(70) Aksglaede L, Olsen LW, Sorensen TI, Juul A. Forty years trends in timing of pubertal growth spurt in 157,000 Danish school children. PLoS One 2008; 3:e2728.

(71) Giustina A, Scalvini T, Tassi C, Desenzani P, Poiesi C, Wehrenberg WB, et al. Maturation of the regulation of growth hormone secretion in young males with hypogonadotropic hypogonadism pharmacologically exposed to progressive increments in serum testosterone. J Clin Endocrinol Metab 1997; 82:1210-1219.

(72) Morishima A, Grumbach MM, Simpson ER, Fisher C, Qin K. Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. J Clin Endocrinol Metab 1995; 80:3689-3698.

(73) Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, Specker B, et al. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med 1994; 331:1056-1061.

(74) Acheson RM, Fowler GB. Sex, Socio-Economic Status, and Secular Increase in Stature, a Family Study. Br J Prev Soc Med 1964; 18:25-34.

(75) Takaishi M. Growth standards for Japanese children – an overview with special reference to secular change in growth. Essays on auxology presented to James Mourilyan Tanner. In: Hauspie R, Lindgren G, Falkner F, editors. Welwyn Garden City: Castlemead Publications; 1995. p. 302-11.

(76) Lindgren GW, Hauspie RC. Heights and weights of Swedish school children born in 1955 and 1967. Ann Hum Biol 1989; 16:397-406.

(77) Aksglaede L, Juul A, Olsen LW, Sorensen TI. Age at puberty and the emerging obesity epidemic. PLoS One 2009; 4:e8450.

(78) Vercauteren M, Susanne C. The secular trend of height and menarche in Belgium: are there any signs of a future stop? Eur J Pediatr 1985; 144:306-309.

(79) Schonbeck Y, Talma H, van Dommelen P, Bakker B, Buitendijk SE, HiraSing RA, et al. The world's tallest nation has stopped growing taller: the height of Dutch children from 1955 to 2009. Pediatr Res 2013; 73:371-377.

(80) Silventoinen K, Sammalisto S, Perola M, Boomsma DI, Cornes BK, Davis C, et al. Heritability of adult body height: a comparative study of twin cohorts in eight countries. Twin Res 2003; 6:399-408.

(81) Roelants M, Hauspie R, Hoppenbrouwers K. References for growth and pubertal development from birth to 21 years in Flanders, Belgium. Ann Hum Biol 2009; 36:680-694.

(82) Wit JM, Ranke MB, Kelnar CJH. ESPE Classification of Paediatric Endocrine Diagnoses. Hormone research 2007; No. 68(Suppl. 2).

(83) Stochholm K, Juul S, Juel K, Naeraa RW, Gravholt CH. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. J Clin Endocrinol Metab 2006;91:3897-3902.

(84) Massa G, Verlinde F, De Schepper J, Thomas M, Bourguignon JP, Craen M, et al. Trends in age at diagnosis of Turner syndrome. Arch Dis Child 2005; 90:267-268.

(85) Husby S, Koletzko S, Korponay-Szabo IR, Mearin ML, Phillips A, Shamir R, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012; 54:136-160.

(86) Telega G, Bennet TR, Werlin S. Emerging new clinical patterns in the presentation of celiac disease. Arch Pediatr Adolesc Med 2008; 162:164-168.

(87) Fasano A. Clinical presentation of celiac disease in the pediatric population. Gastroenterology 2005; 128:S68-73.

(88) Steens RF, Csizmadia CG, George EK, Ninaber MK, Hira Sing RA, Mearin ML. A national prospective study on childhood celiac disease in the Netherlands 1993-2000: an increasing recognition and a changing clinical picture. J Pediatr 2005; 147:239-243.

(89) Garampazzi A, Rapa A, Mura S, Capelli A, Valori A, Boldorini R, et al. Clinical pattern of celiac disease is still changing. J Pediatr Gastroenterol Nutr 2007; 45:611-614.

(90) Bingley PJ, Williams AJ, Norcross AJ, Unsworth DJ, Lock RJ, Ness AR, et al. Undiagnosed coeliac disease at age seven: population based prospective birth cohort study. BMJ 2004; 328:322-323.

(91) Maki M, Mustalahti K, Kokkonen J, Kulmala P, Haapalahti M, Karttunen T, et al. Prevalence of Celiac disease among children in Finland. N Engl J Med 2003; 348:2517-2524.

(92) Ravikumara M, Nootigattu VK, Sandhu BK. Ninety percent of celiac disease is being missed. J Pediatr Gastroenterol Nutr 2007; 45:497-499.

(93) Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA, American College of Gastroenterology. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol 2013; 108:656-76; quiz 677.

(94) Murch S, Jenkins H, Auth M, Bremner R, Butt A, France S, et al. Joint BSPGHAN and Coeliac UK guidelines for the diagnosis and management of coeliac disease in children. Arch Dis Child 2013; 98:806-811.

(95) World Health Organization. Training Course on Child Growth Assessment. Geneva: WHO; 2008.

(96) Mäki P, Wikström K, Hakulinen-Viitanen T, Laatikainen T editors. Terveystarkastukset lastenneuvolassa ja kouluterveydenhuollossa (Methodological guidebook for physical examination in well-baby clinics and school healthcare, in Finnish). Helsinki: Finnish National Institute for Health and Welfare; 2011.

(97) Mäki P, Laatikainen T, Koponen P, Hakulinen-Viitanen T, LATE work group. editors. Lasten ja nuorten terveysseurannan kehittäminen, LATE-hanke (The development of health

monitoring among children and the young, LATE-project, in Finnish). Helsinki: Finnish National Institute for Health and Welfare; 2008.

(98) van Buuren S. Growth references. In: Kelnar C, Savage M, Saenger P, Cowell C, editors. Growth Disorders 2nd Ed.; 2007. p. 165-181.

(99) Cole TJ. The LMS method for constructing normalized growth standards. Eur J Clin Nutr 1990; 44:45-60.

(100) Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. Stat Med 1992; 11:1305-1319.

(101) Stasinopoulos DM, Rigby RA. Generalized Additive Models for Location Scale and Shape (GAMLSS) in R. 2007; 23.

(102) Galton F. Regression towards mediocrity in hereditary stature. J Anthropol Inst 1886; 15:246-63.

(103) Cole TJ. Presenting information on growth distance and conditional velocity in one chart: practical issues of chart design. Stat Med 1998; 17:2697-2707.

(104) Sorva R, Tolppanen EM, Lankinen S, Perheentupa J. Evaluation of childhood growth. Duodecim 1985; 101:465-476.

(105) Flegal KM, Wei R, Ogden C. Weight-for-stature compared with body mass index-for-age growth charts for the United States from the Centers for Disease Control and Prevention. Am J Clin Nutr 2002; 75:761-766.

(106) Graitcer PL, Gentry EM. Measuring children: one reference for all. Lancet 1981; 2:297-299.

(107) Habicht JP, Martorell R, Yarbrough C, Malina RM, Klein RE. Height and weight standards for preschool children. How relevant are ethnic differences in growth potential? Lancet 1974; 1:611-614.

(108) van Buuren S. Effects of selective dropout on infant growth standards. Nestle Nutr Workshop Ser Pediatr Program 2010 ; 65:167-75;65:167-75; discussion 175-9.

(109) Bellizzi MC, Dietz WH. Workshop on childhood obesity: summary of the discussion. Am J Clin Nutr 1999; 70:173S-5S.

(110) Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000; 894:i-xii, 1-253.

(111) Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 2006; 295:1549-1555.

(112) Kautiainen S, Rimpela A, Vikat A, Virtanen SM. Secular trends in overweight and obesity among Finnish adolescents in 1977-1999. Int J Obes Relat Metab Disord 2002; 26:544-552.

(113) Vuorela N, Saha MT, Salo M. Prevalence of overweight and obesity in 5- and 12-year-old Finnish children in 1986 and 2006. Acta Paediatr 2009; 98:507-512.

(114) Must A, Strauss RS. Risks and consequences of childhood and adolescent obesity. Int J Obes Relat Metab Disord 1999; 23 Suppl 2:S2-11.

(115) Hrafnkelsson H, Magnusson KT, Sigurdsson EL, Johannsson E. Association of BMI and fasting insulin with cardiovascular disease risk factors in seven-year-old Icelandic children. Scand J Prim Health Care 2009; 27:186-191.

(116) Freedman DS, Katzmarzyk PT, Dietz WH, Srinivasan SR, Berenson GS. Relation of body mass index and skinfold thicknesses to cardiovascular disease risk factors in children: the Bogalusa Heart Study. Am J Clin Nutr 2009; 90:210-216.

(117) Reilly JJ, Methven E, McDowell ZC, Hacking B, Alexander D, Stewart L, et al. Health consequences of obesity. Arch Dis Child 2003; 88:748-752.

(118) Freedman DS, Sherry B. The validity of BMI as an indicator of body fatness and risk among children. Pediatrics 2009; 124 Suppl 1:S23-34.

(119) Daniels SR, Khoury PR, Morrison JA. The utility of body mass index as a measure of body fatness in children and adolescents: differences by race and gender. Pediatrics 1997; 99:804-807.

(120) Mei Z, Grummer-Strawn LM, Pietrobelli A, Goulding A, Goran MI, Dietz WH. Validity of body mass index compared with other body-composition screening indexes for the assessment of body fatness in children and adolescents. Am J Clin Nutr 2002; 75:978-985.

(121) Skinner AC, Mayer ML, Flower K, Perrin EM, Weinberger M. Using BMI to determine cardiovascular risk in childhood: how do the BMI cutoffs fare? Pediatrics 2009; 124:e905-12.

(122) Thompson DR, Obarzanek E, Franko DL, Barton BA, Morrison J, Biro FM, et al. Childhood overweight and cardiovascular disease risk factors: the National Heart, Lung, and Blood Institute Growth and Health Study. J Pediatr 2007; 150:18-25.

(123) Raitakari OT, Juonala M, Kahonen M, Taittonen L, Laitinen T, Maki-Torkko N, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. JAMA 2003; 290:2277-2283.

(124) Gray JA. New concepts in screening. Br J Gen Pract 2004; 54:292-298.

(125) van Dommelen P, van Buuren S. Methods to obtain referral criteria in growth monitoring. Stat Methods Med Res 2013; 23:369-389

(126) Duggan MB. Anthropometry as a tool for measuring malnutrition: impact of the new WHO growth standards and reference. Ann Trop Paediatr 2010; 30:1-17.

(127) Norris SA, Griffiths P, Pettifor JM, Dunger DB, Cameron N. Implications of adopting the WHO 2006 Child Growth Standards: case study from urban South Africa, the Birth to Twenty cohort. Ann Hum Biol 2009; 36:21-27.

(128) Nuruddin R, Lim MK, Hadden WC, Azam I. Comparison of estimates of under-nutrition for pre-school rural Pakistani children based on the WHO standard and the National Center for Health Statistics (NCHS) reference. Public Health Nutr 2009; 12:716-722.

(129) Lapidus N, Minetti A, Djibo A, Guerin PJ, Hustache S, Gaboulaud V, et al. Mortality risk among children admitted in a large-scale nutritional program in Niger, 2006. PLoS One 2009; 4:e4313.

(130) O'Neill SM, Fitzgerald A, Briend A, Van den Broeck J. Child mortality as predicted by nutritional status and recent weight velocity in children under two in rural Africa. J Nutr 2012; 142:520-525.

(131) Tanner JM, Goldstein H, Whitehouse RH. Standards for Children's Height at Age 2 to 9 years allowing for height of Parents. Arch Dis Child 1970; 45:819.

(132) Wright CM, Cheetham TD. The strengths and limitations of parental heights as a predictor of attained height. Arch Dis Child 1999; 81:257-260.

(133) Hermanussen M, Cole J. The calculation of target height reconsidered. Horm Res 2003; 59:180-183.

(134) Luo ZC, Albertsson-Wikland K, Karlberg J. Target height as predicted by parental heights in a population-based study. Pediatr Res 1998; 44:563-571.

(135) Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000; 320:1240-1243.

(136) Cole TJ, Flegal KM, Nicholls D, Jackson AA. Body mass index cut offs to define thinness in children and adolescents: international survey. BMJ 2007; 335:194.

(137) Fayter D, Nixon J, Hartley S, Rithalia A, Butler G, Rudolf M, et al. Effectivesness and cost-effectiveness of height-screening prorammes during the primary school years: a systematic review. Arch Dis Child 2008; 93:278-284.

(138) Fayter D, Nixon J, Hartley S, Rithalia A, Butler G, Rudolf M, et al. A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions. Health Technol Assess 2007; 11:iii, xi-xii, 1-163.

(139) Agwu JC, Leishenring A, Darnley I. Community growth monitoring in practice. Arch Dis Child 2004; 89:394.

(140) Ahmed ML, Allen AD, Dunger DB, Macfarlane A. The Oxford growth study: a district growth surveillance programme 1988-1994. J Med Screen 1995; 2:160-163.

(141) Banerjee S, Morgan RJ, Rees SA, Latif AH. Height screening at school: ineffective without high standards and adequate resources. Arch Dis Child 2003; 88:477-81; discussion 477-81.

(142) Cernerud L, Edding E. The value of measuring height and weight of schoolchildren. Paediatr Perinat Epidemiol 1994; 8:365-372.

(143) de la Puente ML, Ibanez L, Marcos MV, Peix MA. Primary care population screening for growth. Aten Primaria 1999; 23:346-351.

(144) Hearn S, Cotterill AM, Majrowski W, Rohan C, Jenkins S, Savage MO. Construction of a community height surveillance programme: the Hackney growth initiative. J Med Screen 1995; 2:31-34.

(145) Lacey KA, Parkin JM. Causes of short stature. A community study of children in Newcastle upon Tyne. Lancet 1974; 1:42-45.

(146) Lindsay R, Feldkamp M, Harris D, Robertson J, Rallison M. Utah Growth Study: growth standards and the prevalence of growth hormone deficiency. J Pediatr 1994; 125:29-35.

(147) Vimpani GV, Vimpani AF, Pocock SJ, Farquhar JW. Differences in physical characteristics, perinatal histories, and social backgrounds between children with growth hormone deficiency and constitutional short stature. Arch Dis Child 1981; 56:922-928.

(148) Voss LD, Mulligan J, Betts PR, Wilkin TJ. Poor growth in school entrants as an index of organic disease: the Wessex growth study. BMJ 1992; 305:1400-1402.

(149) Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser 1995; 854:1-452.

(150) Ministry of Social Affairs and Health. Primary healthcare act 66/1972, Goverment degree on primary health care 380/2009.

(151) Massa GG, Vanderschueren-Lodeweyckx M. Age and height at diagnosis in Turner syndrome: influence of parental height. Pediatrics 1991; 88:1148-1152.

(152) Espoon keskushallinto, hallintokeskus, kehittämis- ja tutkimusryhmä. Paakko S. (ed.). Espoon kaupungin tilastollinen vuosikirja 2007. Kirjapaino, Espoo 2008: 21-40a

(153) Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, Ross JL, et al. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. J Clin Endocrinol Metab 2008; 93:4210-4217.

(154) Royston P, Altman DG. Using fractional polynomials to model curved regression relationships. Stata Tech Bull 1994:11-23.

(155) Sankilampi U, Hannila ML, Saari A, Gissler M, Dunkel L. New population-based references for birth weight, length, and head circumference in singletons and twins from 23 to 43 gestation weeks. Ann Med 2013; 45:446-454.

(156) Borghi E, de Onis M, Garza C, Van den Broeck J, Frongillo EA, Grummer-Strawn L, et al. Construction of the World Health Organization child growth standards: selection of methods for attained growth curves. Stat Med 2006; 25:247-265.

(157) Erkkola M, Salmenhaara M, Kronberg-Kippila C, Ahonen S, Arkkola T, Uusitalo L, et al. Determinants of breast-feeding in a Finnish birth cohort. Public Health Nutr 2009; 13:1-10.

(158) Verkasalo M. Recent trends in breast-feeding in Southern Finland. Acta Paediatr Scand 1980; 69:89-91.

(159) Salmenpera L, Perheentupa J, Siimes MA. Exclusively breast-fed healthy infants grow slower than reference infants. Pediatr Res 1985; 19(3):307-312.

(160) Sorensen K, Aksglaede L, Petersen JH, Juul A. Recent changes in pubertal timing in healthy Danish boys: associations with body mass index. J Clin Endocrinol Metab 2010; 95:263-270.

(161) Cole TJ. A method for assessing age-standardized weight-for-height in children seen cross-sectionally. Ann Hum Biol 1979; 6:249-268.

(162) US Preventive Services Task Force, Barton M. Screening for obesity in children and adolescents: US preventive services task force recommendation statement. Pediatrics 2010; 125:361-367.

(163) Gozzi T, Fluck C, L'allemand D, Dattani MT, Hindmarsh PC, Mullis PE. Do centimetres matter? Self-reported versus estimated height measurements in parents. Acta Paediatr 2010; 99:569-574.

(164) Meazza C, Pagani S, Laarej K, Cantoni F, Civallero P, Boncimino A, et al. Short stature in children with coeliac disease. Pediatr Endocrinol Rev 2009; 6: 457-463.

(165) Bonamico M, Scire G, Mariani P, Pasquino AM, Triglione P, Scaccia S, et al. Short stature as the primary manifestation of monosymptomatic celiac disease. J Pediatr Gastroenterol Nutr 1992; 14:12-16.

(166) de Lecea A, Ribes-Koninckx C, Polanco I, Calvete JF. Serological screening (antigliadin and antiendomysium antibodies) for non-overt coeliac disease in children of short stature. Acta Paediatr Suppl 1996; 412:54-55.

(167) van Rijn JC, Grote FK, Oostdijk W, Wit JM. Short stature and the probability of coeliac disease, in the absence of gastrointestinal symptoms. Arch Dis Child 2004; 89:882-883.

(168) Ludvigsson JF, Ansved P, Falth-Magnusson K, Hammersjo JA, Johansson C, Edvardsson S, et al. Symptoms and signs have changed in Swedish children with coeliac disease. J Pediatr Gastroenterol Nutr 2004; 38:181-186.

(169) Savilahti E, Kolho KL, Westerholm-Ormio M, Verkasalo M. Clinics of coeliac disease in children in the 2000s. Acta Paediatr 2010; 99:1026-1030.

(170) Korponay-Szabo IR, Szabados K, Pusztai J, Uhrin K, Ludmany E, Nemes E, et al. Population screening for coeliac disease in primary care by district nurses using a rapid antibody test: diagnostic accuracy and feasibility study. BMJ 2007; 335:1244-1247.

(171) van Dommelen P, Grote FK, Oostdijk W, Keizer-Schrama SM, Boersma B, Damen GM, et al. Screening rules for growth to detect celiac disease: a case-control simulation study. BMC Pediatr 2008; 8:35-2431-8-35.

(172) Leino T, Koskenniemi E, Saranpää P, Strömberg N, Kilpi T. Rokotuskattavuus edelleen huippuluokkaa. SLL 2007; 62:739-742.

(173) Bates DW, Leape LL, Cullen DJ, Laird N, Petersen LA, Teich JM, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. JAMA 1998; 280: 1311-1316.

(174) Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. Arch Intern Med 2003; 163:1409-1416.

Antti Saari

Modern methods for auxological screening of growth disorders in children

The general aims of this thesis was to up-date Finnish growth references and create new, evidence-based tools for auxological screening of growth disorders in children. Up-dated national growth references were found accurate for growth monitoring, and early detection of two target condition, Turner syndrome and celiac disease, could be facilitated in novel auxological screening methods for attained height and weight. In addition, automated growth monitoring process and consultation service was found to be distinctly better than its manually orientated counterpart in primary care. Modern methods for growth monitoring in children are now ready for implementation in the healthcare system.

UNIVERSITY OF
EASTERN FINLAND

Publications of the University of Eastern Finland
Dissertations in Health Sciences

ISBN 978-952-61-1723-2