

POPULATION STUDY ARTICLE



Growth pattern evaluation of the Edinburgh and Gothenburg cohorts by QEPS height model

Anton Holmgren^{1,2✉}, Aimon Niklasson¹, Andreas F. M. Nierop^{3,4}, Gary Butler⁵ and Kerstin Albertsson-Wikland³

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BACKGROUND: The QEPS-growth-model, developed and validated in GrowUp-Gothenburg cohorts, used for developing growth references and investigating healthy/pathological growth, lacks external validation from other longitudinal cohorts of healthy individuals.

AIM: To investigate if the QEPS-model can fit the longitudinal Edinburgh growth study of another design than GrowUp-Gothenburg cohorts, and to compare growth patterns in the individuals born in mid-1970s in North-Western Europe.

METHODS: Longitudinal growth data were obtained from the Edinburgh and the GrowUp1974Gothenburg cohorts. The QEPS-model was used to describe length/height from birth to adult height with confidence interval, and the multivariable regression model for estimating the contribution of the different QEPS-functions to adult height.

RESULTS: The QEPS-model fitted the Edinburgh cohort well, with high accuracy, and low confidence intervals indicating high precision. Despite 3 cm shorter stature (less QE-function growth) in Scottish children, the growth patterns of the cohorts were similar, especially for specific pubertal growth. The contribution to adult height from different QEPS functions was similar.

CONCLUSION: The QEPS-model is validated for the first time in a longitudinal study of healthy individuals of another design and found to fit with high accuracy and precision. The Scottish and Western-Swedish cohorts born in mid-1970s showed similar growth patterns for both sexes, especially pubertal growth.

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IMPACT:

- For the first time, the QEPS height model was used and found to fit another longitudinal cohort of healthy individuals other than the Swedish longitudinal cohorts.
- With large numbers of individual measurements in each growth phase, the QEPS model calculates growth estimates with narrow confidence intervals (high precision) and high accuracy.
- The two different cohorts born in the mid-1970s from Scotland and Western Sweden have similar growth patterns, despite a 3 cm difference in adult height.

INTRODUCTION

Growth patterns are dynamic processes both for the developing individual and at the population level over time. Patterns of growth differ between individuals, sexes, and populations and these rhythms change with time, due to the importance of both genes and environmental factors.¹ Human growth can be described as the different trajectories of height that runs from birth until attained adult height by different periods of acceleration, deceleration, and linear growth. These periods are linked to distinct biological growth phases, infancy, childhood, and puberty, and under separate influences: nutrition in infancy, growth hormone (GH) dose-dependent growth during childhood, and by the addition of an interplay of sex steroids during puberty.^{2,3} The transition between each of these growth phases may be associated with increased

cellular plasticity and the activation of the hormone axis that regulates the growth during the subsequent phase.^{2,3} The total growth in height includes rapid fetal growth before birth, a rapid but also steeply declining velocity during the infancy growth period, and a long steady period of childhood growth followed by the pubertal growth spurt.¹ Growth during puberty is manifested by acceleration followed by deceleration until adult height is reached. A child with a growth pattern that deviates from the mean of the population may suffer from a disease or have psychosocial problems; hence, the importance and attention required to the measuring of growth in pediatric practice.^{1,4} Over the last decade, humans in affluent countries have become progressively taller and puberty and the pubertal growth spurt has started earlier.^{1,5–7} These changes are referred as secular changes or trends.^{5,8,9}

¹GP-GRC, Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. ²Department of Pediatrics, Halmstad Hospital, Halmstad, Sweden. ³Department of Physiology/Endocrinology, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. ⁴Muvara bv, Multivariate Analysis of Research Data, Leiderdorp, The Netherlands. ⁵UCL Great Ormond Street Institute of Child Health, and University College London Hospital, London, UK. ✉email: anton.holmgren@regionhalland.se

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The classic European and US growth studies have been longitudinal studies, in which every child was measured repeatedly, improving the value of the conclusions from such studies.^{10–13} When studying growth with more frequent than annual measurements in each individual, some growth studies find both seasonal variations and a mid-childhood growth spurt.^{14–17}

At a very detailed level, differences in heights during the day can be seen (diurnal variation), where an individual is 5–15 mm shorter during the evening compared with the morning.^{18–20} Diurnal variation may have relevance in clinical practice when children with chronic diseases are measured repeatedly at very frequent intervals. No growth model has yet been developed to describe adequately the short time variations of growth over time such as seasonal variations or the mid-childhood growth spurts.

When studying growth patterns from birth to attained adult height with the different growth phases, recognized to be under different influences, it may be beneficial to have a research tool describing growth using separate phase functions.^{21,22} Only two growth models have been developed which can describe growth from birth until adult height with these different mathematic growth functions: the infancy–childhood–puberty (ICP) and the QEPS models.^{21,22} The QEPS growth model was partly based on ideas from the ICP model and can be used to illustrate the whole pattern of growth, as well as the different phases of growth in a standardized way.²² Based on measurements of height for an individual, the model generates an individual growth curve. The QEPS model uses four growth-related functions, *Q* (quadratic), *E* (exponential), *P* (puberty), and *S* (stop), where the combination of these functions, *T* (total), explains growth from fetal life to adult height. Due to the specific pubertal growth function, it is possible to define the onset, middle, and end of pubertal growth mathematically. The model also calculates individual confidence intervals (CIs) for the growth estimates that can be used to evaluate precision, the reliability of measurements, and estimates, as a quality check for the generated individual growth curve.^{22,23} The QEPS model was developed using reference growth data from the community-based population study, GrowUp 1974 Gothenburg cohort.²⁴ The model was later validated using the individual data of 1974 and also with GrowUp 1990 Gothenburg cohort.^{9,25}

There remains the need to validate the QEPS model in another setting and investigate how the growth estimates by QEPS can describe growth patterns in a growth study and dataset that differs from the sources used in previous publications.

The aims of the present study were:

1. To investigate if the QEPS growth model was suitable to fit the longitudinal Edinburgh growth cohort measurements.
2. To study similarities and differences in growth patterns of individuals born in North Western Europe in mid-1970s from two longitudinal growth studies.

Thus, this study used longitudinal growth data obtained from two cohort studies, the GrowUp 1974 Gothenburg cohort, which forms the basis of the current Swedish growth reference from which the QEPS model was developed, and the Edinburgh longitudinal growth study.^{14,24,26–28}

MATERIALS AND METHODS

Ethical approval

Subjects in the Edinburgh cohort were recruited in accordance with the UK Medical Research Council Guidelines for ethical research in children at that time.^{27,28} For subjects in the Gothenburg cohort, ethical approval was obtained from the Regional Ethics Review Board in Gothenburg (Ad 91-92/131-93 and 444-08 T062-09), and all participants gave informed consent (informed consent from legal guardians was given for individuals <18 years of age).

Study design

Growth characteristics of two different longitudinal followed birth cohorts from Edinburgh, Scotland and Gothenburg, western Sweden,^{14,24,26–28} born in the mid-1970s, were compared by applying the QEPS growth model.^{22,23}

Study subjects

Edinburgh Longitudinal Growth Study. This group consisted of children born between 1972 and 1976 as singletons with birthweight above 2.5 kg and chromosome karyotype 46, XY or 46, XX. Gestational age was not recorded. They form part of the control group for the study of growth and development in children with sex chromosome aneuploidy.²⁷ All the children were healthy, without chronic diseases and lived in a normal environment without social deprivation. The children attended the Growth Clinic every third month until 1 year of age and thereafter until adult height at six monthly intervals around the time of their birthday and at the half yearly point. A specially trained team completed a full range of anthropometric measures using the equipment and techniques identical to those used in the Harpenden Study.¹⁰ The study group has been described in detail elsewhere.^{14,27,28} The cohort comprised 177 children, 74 girls and 103 boys. Excluded for the present analyses were 20 children, 6 girls and 14 boys, due to either lacking measurements during childhood or uncertainty whether adult height had been reached. Thus, the present analysis included data from 157 healthy individuals (68 girls, 89 boys), with growth data evenly distributed through all ages, median of 34 measurements for girls, 37 for boys with a median age of 7.6/8.5 years for girls and boys (Fig. 1).

GrowUp 1974 Gothenburg cohort. The study group from the GrowUp 1974 Gothenburg cohort consisted of a subgroup of healthy individuals born at full term (gestational age: 37–42 weeks) around 1974 in Sweden, for whom information on longitudinal growth until adult height was available. Height and weight had been measured at well-baby clinics, child healthcare centers, and at school. A specially trained team measured the students in their 11th school year, at 17–18 years of age. Height was measured using a calibrated Harpenden stadiometer. Individuals who were still growing were followed with additional measurements by the study team until adult height was attained. The study populations and selection procedures have been described in detail elsewhere.^{23,24} The present study included data from 2339 healthy individuals (1165 girls). Growth data were most frequently collected in the first 6 years of life. Between 6 and 18 years of age most individuals were measured at 2–3-year intervals. There was a median of 22 measurements per individual (same for both sexes) with a median age for both sexes of 2.0 years (Fig. 1).

The QEPS growth model

The QEPS model was used to describe individual patterns of growth in terms of length/height from birth to adult height. Growth in height is modelled by a Quadratic (*Q*) function, a negative Exponential (*E*) function, a specific Pubertal (*P*) function, and a Stop (*S*) function (Fig. 2), for more detailed information see previous publications.^{22,23} The total height (*T*) in cm is a function of age: $T(\text{age}) = Q(\text{age}) + E(\text{age}) + P(\text{age}) - S(\text{age})$. The different growth functions can be modified for *E* and *P* by both timescale and height-scale parameters, and for *Q* and *S* by height-scale parameters, thus describing individualized growth with a shape-invariant model. Separate curve fitting for each individual gives six estimates with confidence intervals (CI) and the possibility to compute many derived variables and individual QEPS function values at all ages. The QEPS model can separate growth during puberty, the specific pubertal *P*-function growth, from the ongoing basic (*QE*-function) of growth and thus describe the total gain (called *TgainP5-95*) in height during puberty, as well as the specific gain in adult height related to puberty (*Pmax*). The onset of pubertal growth was defined as the age at which 5% of *P*-function growth was attained (*AgeP5*). The middle of puberty was defined as the age at which 50% of *P*-function growth was attained (*AgeP50*). The more traditional measure of the middle of puberty, age at PHV, was calculated from the total growth curve (*AgeTPHV*). The end of pubertal growth was defined as the age at which 95% of *P*-function growth had been completed (*AgeP95*).²³ The duration of growth during puberty was calculated as the time from *AgeP5* to *AgeP95*, and the total gain during this period can be separated into ongoing basic growth, *QESgain*, and specific pubertal growth, *Pgain* (Fig. 2).

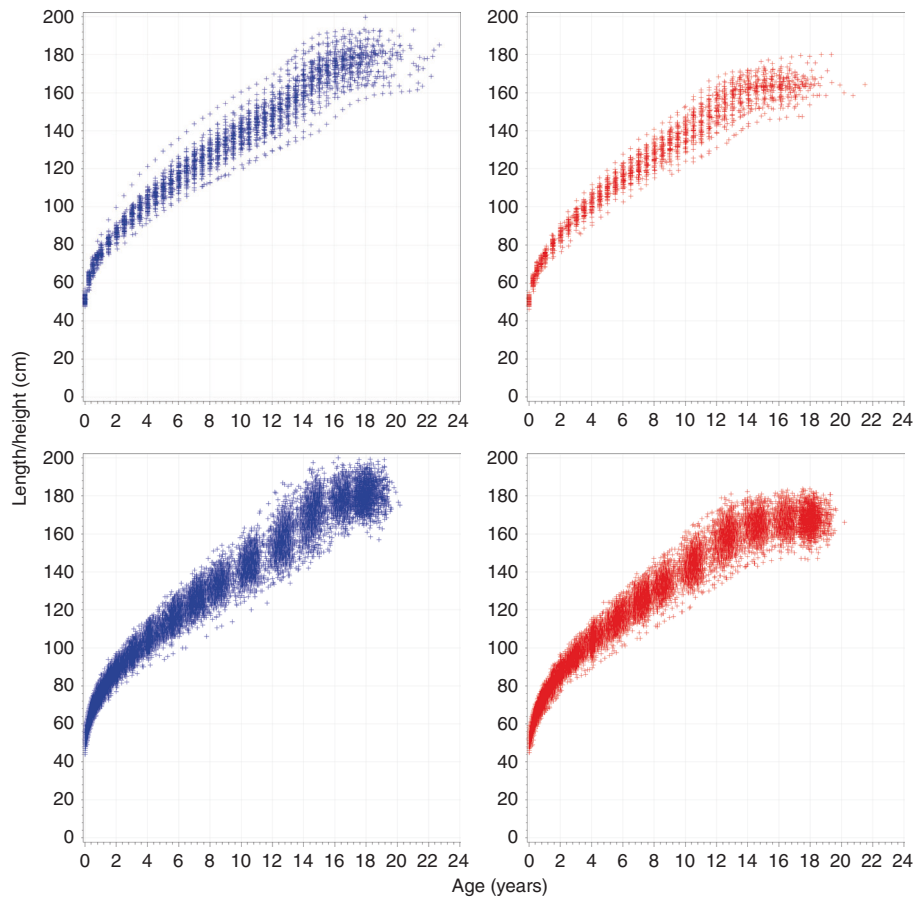


Fig. 1 Distribution of length/height by age of the Edinburgh and GrowUp 1974 Gothenburg longitudinal cohorts. Distribution of length/height by age (upper panel Edinburgh longitudinal cohort, lower panel GrowUp 1974 Gothenburg cohort; male, left and blue; female, right and red). The different study design is presented with fewer individuals in the Edinburgh cohort but with both shorter and more regular time intervals. In dense areas points overlap. The median age at measurements were 7.6/8.5 years (girls/boys) in the Edinburgh cohort and 2.0 years (both sexes) in the Gothenburg cohort. For the QEPS analyses there were a median of 34 individual measurements for girls, 37 for boys in the Edinburgh cohort (range 14–44), and 23 measurements (range 11–61) in the Gothenburg cohort (same median for both sexes).

Data handling and statistical analysis

To construct longitudinal growth curves for each individual in the two study groups, height data were exported to Matlab®, and QEPS model parameters were automatically estimated by fitting the height data from each individual separately (The MathWorks, Inc., Natick, MA, USA, v. 9.3.0 R2017b). Some individuals were excluded from further analyses due to lack of measurements at all age periods or due to uncertainty regarding if adult height was reached. The selected individuals in the Edinburgh growth cohort were treated as if born at 40 weeks gestational age. Student's two-tailed *t*-test was used to compare birth characteristics and growth estimates from the QEPS growth model for the Edinburgh and Gothenburg growth cohorts (normal distributed data/estimates). Statistical analyses were performed using SAS software® (SAS Institute Inc., Cary, NC, USA, version 9.3). A *p* value <0.05 was considered statistically significant.

Multivariable regression analyses concerning how the QEPS model estimates explained variation in adult height were performed for the two growth cohorts, separate for each sex. The growth functions *E*_{max}, *Q*_{max}, *P*_{max}, and *AgeP50* were analyzed. For pubertal timing, *AgeP50* was selected because of the lowest CI (Table 1).

RESULTS

Confidence intervals (CIs) for precision and standard error for accuracy

There was a clear difference between the cohorts with lower CIs in the Edinburgh study group for all QEPS estimates (Table 1). The main QEPS-height estimates (*E*_{max}, *Q*_{max}, *P*_{max}) had CIs of just 1.1–2.1 cm in the Edinburgh cohort compared with 1.9–4.3 cm in the Gothenburg group. There was a difference between the sexes

with higher CIs in girls for QEPS estimates in both cohorts. For both sexes, the CIs for onset of pubertal growth, *AgeP5*, were broader than for the mid-pubertal growth, *AgeP50* (Table 1). The mean standard error of the fit for the Edinburgh cohort for girls/boys was 0.68/0.80 cm versus 0.97/1.02 cm for the Gothenburg cohort (Table 1).

Comparison of growth characteristics for infant and childhood growth

The girls and boys in the Edinburgh cohort were significantly longer at birth (both *p* < 0.0001) than those from the Gothenburg cohort (Table 2). There were no significant differences between the study groups for weight at birth. The tempo of growth, mainly during infancy (*E*_{timescale}), the gain in height due to *E*-function growth (*E*_{max}) and the continuing growth function from before birth until adult height, mainly characterizing childhood growth (*Q*_{max}) were compared. Growth during the fetal/infancy period was more rapid in the Edinburgh compared with the Gothenburg cohort as shown by a significantly shorter *E*_{timescale} for both girls and boys. The total *E*-growth (*E*_{max}) was 1.1–1.5 cm lower in the Edinburgh study group (Table 2 and Fig. 3). The *Q*_{max} was also lower in the Edinburgh study group with a difference of 1.4–1.8 cm (girls/boys) compared with the Gothenburg cohort, with a significant difference in *Q*_{max} and *Q* height velocity for boys (Table 2, Fig. 3 and Supplementary Fig. S1). The total QEPS-calculated height was greater in the Gothenburg cohort after around 6–9 months of age as seen in Figs. 3 and 4.

Comparison of growth characteristics for pubertal growth

In general, the pubertal growth patterns between the two study groups were very similar (Table 3, Figs. 3, 5 and Supplementary Fig. S1). The timing of pubertal growth, including the ages at the start (*AgeP5*), middle (*AgeP50* and *AgeTPHV*), and end (*AgeP95*) of pubertal growth, showed no statistical differences between the

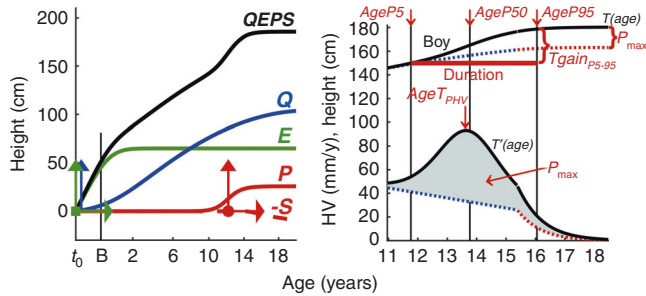


Fig. 2 The QEPS growth model. Left: The four mathematical functions of the QEPS model that are combined to describe total gain in height (*T*) from fetal life to adulthood: Quadratic (*Q*), Exponential (*E*), Pubertal (*P*), and Stop (*S*). *B* = birth, marked with a vertical line. *t0* = about 6 weeks after conception. The three vertical arrows indicate the fitted individual height-scale parameters, from left to right *Eheightscale*, *Qheightscale*, and *Pheightscale*. The two horizontal arrows indicate the time-scale parameters, from left to right *Etimescale* and *Ptimescale*, and the sixth parameter is the location of mid puberty, *AgeP50*, indicated with a dot. Right: Total height and height velocity estimated by the QEPS model are shown for an individual. Onset, *AgeP5* as age at which 5% of the *P*-function growth is reached; mid puberty, *AgeP50* as age at which 50% of the *P*-function growth is reached and age at peak height velocity *AgeTPHV*, of the total height function *T* from the QEPS model is reached; and end of pubertal growth, *AgeP95* as age at which 95% of the *P*-function growth is reached are marked with vertical lines. The duration of puberty is shown by the bold horizontal line. The pubertal height gain is shown as the growth from *AgeP5* to *AgeP95* from the total growth curve (*TgainP5-95*), and from the specific pubertal part (*Pmax*); both shown at the top of the figure in the height graph and *Pmax* as the marked area in the height velocity graph.

two study groups. For girls, the duration of pubertal growth was about 1.5 months shorter in the Edinburgh cohort (Table 3). The specific *P*-function growth *Pmax* did not differ between the cohorts for boys. The total pubertal growth for boys, (*Tgain* from *AgeP5* to *AgeP95*) was higher (0.9 cm) in the Gothenburg cohort due to more basic growth (*QES-gain*) during this period (Table 3).

Both sexes in the Gothenburg cohort had significantly greater attained heights at the onset of puberty (height at *AgeP5*) and in mid puberty (height at *PHV*). At the end of puberty, the resulting calculated adult heights by the QEPS-model (*Tmax*) were significant higher for both sexes in the Gothenburg cohort, in girls +2.8 cm, 167.3 vs 164.4 cm, and in boys +2.9 cm, 180.5 vs 177.7 cm (Table 3 and Figs. 3 and 4).

Contribution of the QEPS-functions for explaining variation in adult height

Using multivariable regression analyses for explaining the variation in adult height, the combination of *Emax* and *Qmax* explained 59–70%, of which *Emax* contributed with 5–12% and *Qmax* with 42–58% (Table 4). Addition of *Pmax* expanded the explanation to 78–91% and, timing of pubertal growth, here as *AgeP50*, added the remaining explanation, ending up in 98.4–99.5% of explaining the variance of adult height (Table 4).

DISCUSSION

General findings

For the first time, the QEPS model was used to analyze another longitudinal cohort of healthy individuals other than the Swedish longitudinal cohorts. Although the QEPS model is a relatively rigid shape-invariant model it appeared to fit the individual growth data of the Edinburgh cohort well with even lower CIs than in the Gothenburg cohort, due to a narrower time interval between the measurements obtained across the whole age range. Using the estimates of the QEPS model we were able to characterize differences and similarities in growth patterns between the two longitudinal growth cohorts born in Edinburgh and Gothenburg in the mid-1970s. As a methodological study, the present paper shows the validity of the QEPS-model in another kind of study

Table 1. The confidence intervals for QEPS estimates.

(A)	Gothenburg cohort, girls (n 1165)			Edinburgh cohort, girls (n 68)			Difference	P value
	Mean	SD	95% CI	Mean	SD	95% CI		
<i>TSDerror</i>	0.97	0.24	0.96–0.98	0.68	0.15	0.64–0.71	0.29	<0.0001
<i>EmaxCI</i>	2.10	0.73	2.05–2.14	1.14	0.34	1.06–1.22	0.96	<0.0001
<i>QmaxCI</i>	4.25	1.41	4.17–4.33	2.11	0.68	1.95–2.28	2.14	<0.0001
<i>PmaxCI</i>	2.82	0.87	2.77–2.87	1.22	0.41	1.12–1.32	1.60	<0.0001
<i>TmaxCI</i>	1.45	0.46	1.42–1.47	0.78	0.31	0.71–0.85	0.67	<0.0001
<i>AgeP5CI</i>	0.90	0.37	0.88–0.92	0.42	0.18	0.38–0.47	0.72	<0.0001
<i>AgeP50CI</i>	0.55	0.22	0.53–0.56	0.22	0.10	0.20–0.25	0.33	<0.0001
(B)	Gothenburg cohort, boys (n 1174)			Edinburgh cohort, boys (n 89)			Difference	P value
	Mean	SD	95% CI	Mean	SD	95% CI		
<i>TSDerror</i>	1.02	0.26	1.01–1.04	0.80	0.21	0.75–0.84	0.22	<0.0001
<i>EmaxCI</i>	1.95	0.66	1.91–1.98	1.09	0.31	1.02–1.16	0.86	<0.0001
<i>QmaxCI</i>	3.92	1.26	3.84–3.99	1.96	0.58	1.84–2.08	1.96	<0.0001
<i>PmaxCI</i>	2.63	0.76	2.58–2.67	1.19	0.40	1.11–1.27	1.44	<0.0001
<i>TmaxCI</i>	1.86	0.63	1.83–1.90	0.97	0.46	0.87–1.07	0.89	<0.0001
<i>AgeP5CI</i>	0.73	0.28	0.72–0.75	0.34	0.11	0.32–0.36	0.39	<0.0001
<i>AgeP50CI</i>	0.43	0.16	0.42–0.44	0.19	0.07	0.17–0.20	0.24	<0.0001

Standard error of the fit of the total height function (*TSDerror*) and confidence intervals (CIs) for the QEPS growth estimates. Difference is the difference between the mean values.

Table 2. Comparison of growth characteristics for infant and childhood growth.

(A)	Gothenburg cohort, girls (n 1165)			Edinburgh cohort, girls (n 68)			Difference	P value
	Mean	SD	95% CI	Mean	SD	95% CI		
Birth weight (kg)	3.41	0.47	3.38–3.44	3.36	0.34	3.28–3.45	0.05	0.42
Birth length (cm)	49.95	2.01	49.83–50.07	51.15	1.78	50.72–51.58	–1.20	<0.0001
Gestational age (weeks)	39.79	1.02	39.73–39.84	n.a.	n.a.	n.a.	n.a.	n.a.
Max value of <i>E</i> -function (cm)	62.85	2.87	62.69–63.02	61.40	2.53	60.78–62.01	1.45	<0.0001
<i>E</i> timescale ^a	1.01	0.10	1.01–1.02	0.92	0.08	0.90–0.94	0.09	<0.0001
Max value of <i>Q</i> -function (cm)	97.59	7.56	97.16–98.03	96.21	7.11	94.49–97.93	1.38	0.14
(B)	Gothenburg cohort, boys (n 1174)			Edinburgh cohort, boys (n 89)			Difference	P value
Variable	Mean	SD	95% CI	Mean	SD	95% CI		
Birth weight (kg)	3.52	0.48	3.49–3.54	3.49	0.42	3.40–3.58	0.03	0.59
Birth length (cm)	50.53	2.10	50.41–50.65	51.79	1.88	51.39–52.18	–1.26	<0.0001
Gestational age (weeks)	39.69	1.08	39.62–39.75	n.a.	n.a.	n.a.	n.a.	n.a.
Max value of <i>E</i> -function (cm)	65.07	2.88	64.90–65.23	63.95	2.83	63.35–64.54	1.12	<0.0001
<i>E</i> timescale ^a	1.01	0.09	1.00–1.01	0.92	0.10	0.90–0.94	0.09	<0.0001
Max value of <i>Q</i> -function (cm)	104.05	8.04	103.59–104.51	102.26	7.50	100.68–103.84	1.79	0.042

Difference is the numerical difference between the mean values.

^aTempo of *E*-function growth, modifying the time scale of the *E*-function growth. A shorter *E*timescale means that the *E*max is reached at an earlier age, and is thereby related to being taller in infancy/early childhood.

design, since QEPS until now, with one exception, has been used in Swedish longitudinal growth studies.^{9,23,25,29–31}

The use of confidence intervals for assessing quality of data

Using CIs as a quality marker for human growth has rarely been done before, despite the widespread use of CIs to show the quality of data in other kind of research. Information of CIs of QEPS estimates makes it possible to visualize the precision of estimates for each individual, hence validating the growth data for each individual and as aggregated mean values of CI showing the usefulness of collecting longitudinal growth data in a study population.²³ In general, the Edinburgh study group had very low CIs for all QEPS estimates, highly significantly lower than those from the Gothenburg cohort ($p < 0.0001$). The results were most likely to be due to the differences in study design, with a narrower time interval between measurements in the Edinburgh cohort compared with the Gothenburg cohort.

The relatively lower difference in *E*maxCI of about 0.9 cm between the two cohorts compared with other estimates could be explained by the more frequent measurements of the Gothenburg individuals during the first two–three years of life since *E*max mainly describes growth during the first years of life. As seen before in the Gothenburg cohort, there was a difference between the sexes with higher CIs for girls of pubertal growth estimates and this was also seen in the Edinburgh cohort.²³ This confirms that a higher *P*max is related to lower CIs of pubertal growth estimates, or explained without QEPS terminology, the higher the magnitude of the pubertal growth spurt, the more precision there is in the definition of the start of the growth spurt and of the age at PHV. Furthermore, the standard error of the fit was used to evaluate the quality of the modelling, with significantly lower values (higher accuracy) in the Edinburgh cohort.

Growth characteristics during the fetal/infancy and childhood growth periods

During the infancy growth period there were significant differences between the two cohorts. The Edinburgh newborns were longer at birth with a mean of more than 51 cm for both sexes. This is a clear difference from the Gothenburg newborns and also different from reference populations in other studies/references,^{24,32–36} except for the former Danish reference (from

the early 1970s).^{7,37} Since the exact gestational age was unknown, we applied a value of 40 weeks to all participants in the Edinburgh cohort. Since the birth weights of the Edinburgh newborns were similar to birth weights in the Gothenburg cohort and other growth cohorts, a general later gestational age in the Edinburgh cohort is an unlikely explanation.^{24,32–37} It may instead, at least partly, be due to methodological differences where the newborns in the Edinburgh cohort and perhaps also in the former Danish reference were stretched more by the measuring study-personnel than in the community-based population, the Gothenburg cohorts.

The tempo estimate *E*timescale, mainly representing fetal/infancy period of growth was shorter for both sexes in the Edinburgh compared with Gothenburg cohort, which is in line with more growth before birth (and longer length at birth). However, this finding should be interpreted with caution on account of the likely methodological differences in length at birth between the study groups. The lower total gain in *E*-function growth, *E*max, was consistent with shorter heights during infancy/early childhood in the Edinburgh cohort. In the total growth curve (*T*-function by QEPS), statistical differences in height were seen from around 6–9 months of age and onwards for both sexes. *Q*-function growth, *Q*max, representing mainly childhood growth, is important for assessing achieved heights during childhood. This growth function was also lower in the Edinburgh boys, however not significantly lower in the 68 Edinburgh girls. The 1.9–2.2 cm greater height in the Gothenburg boys and girls at the onset of puberty (*AgeP5*) occurred on account of both the higher *E*- and *Q*-functions.

Characteristics of pubertal growth and adult height

The QEPS model offers a unique possibility to analyze pubertal growth (*P*-function). There was a striking similarity in pubertal growth patterns between the two cohorts, despite the geographical differences and the different kind of data sets used, with relatively few measurements for each individual during the adolescent years in the Gothenburg cohort. There were no major differences in the estimates of the specific pubertal growth function. The comparison between the Edinburgh and Gothenburg in respect of the timing and amount of pubertal growth showed a greater similarity than between the two Swedish growth

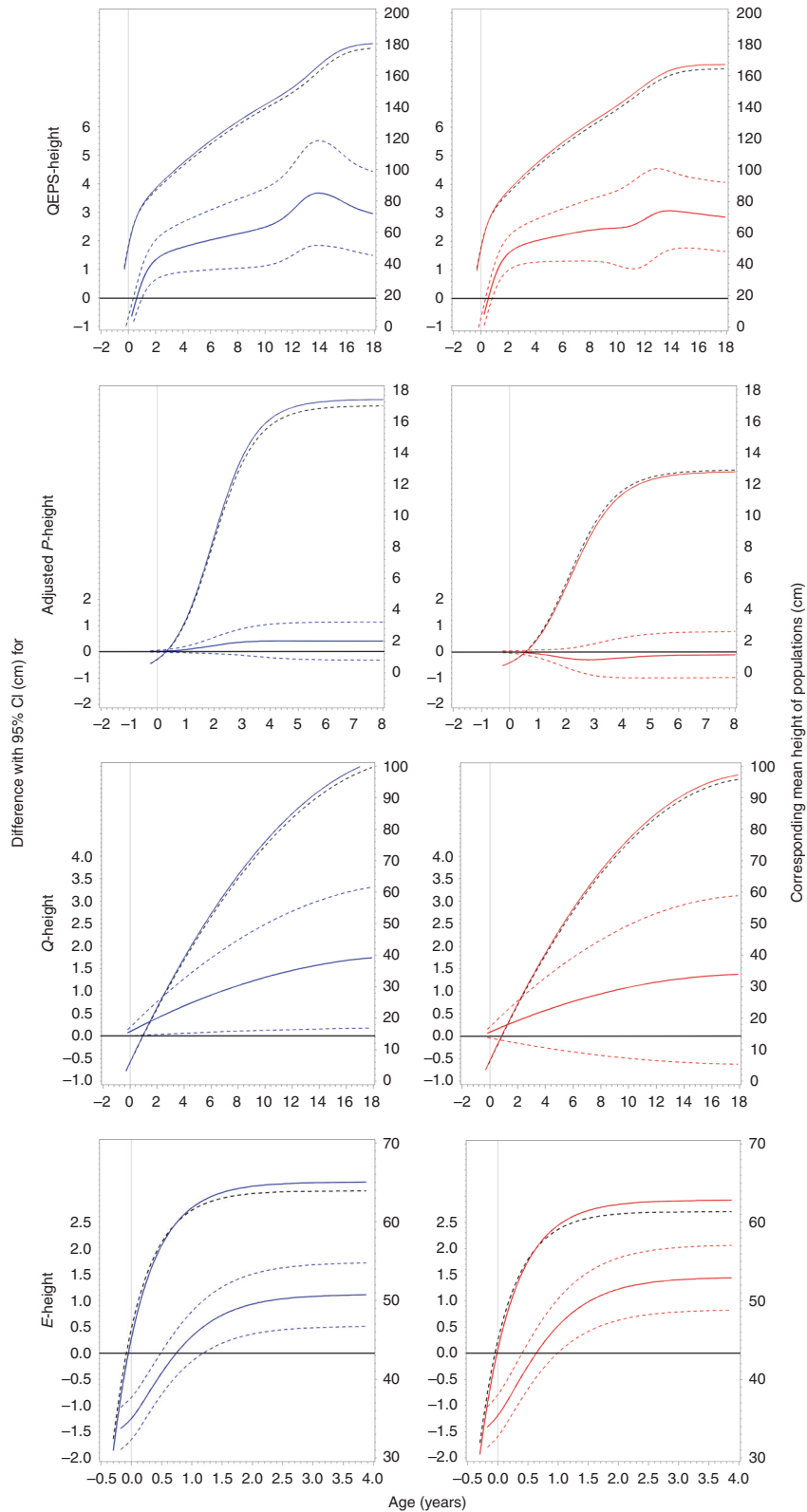


Fig. 3 The difference between the means of various QEPS height functions (bold solid lines) for Gothenburg minus Edinburgh cohorts with the 95% confidence interval (bold broken lines) on the left axis. Boys (blue to the left) and girls (red to the right). This means that if the confidence interval includes the zero line there is no significant difference between the mean lines at that age point. For comparison the mean lines (Gothenburg solid line, Edinburgh black dotted line) are depicted on the right axis. The height functions from above to below; total QEPS height function (*T*), pubertal height function (*P*), quadratic height function (*Q*), and exponential height function (*E*). Note that for the *P*-function, adjusted age for puberty is used, whereas for all other functions in relation to chronological age (years).

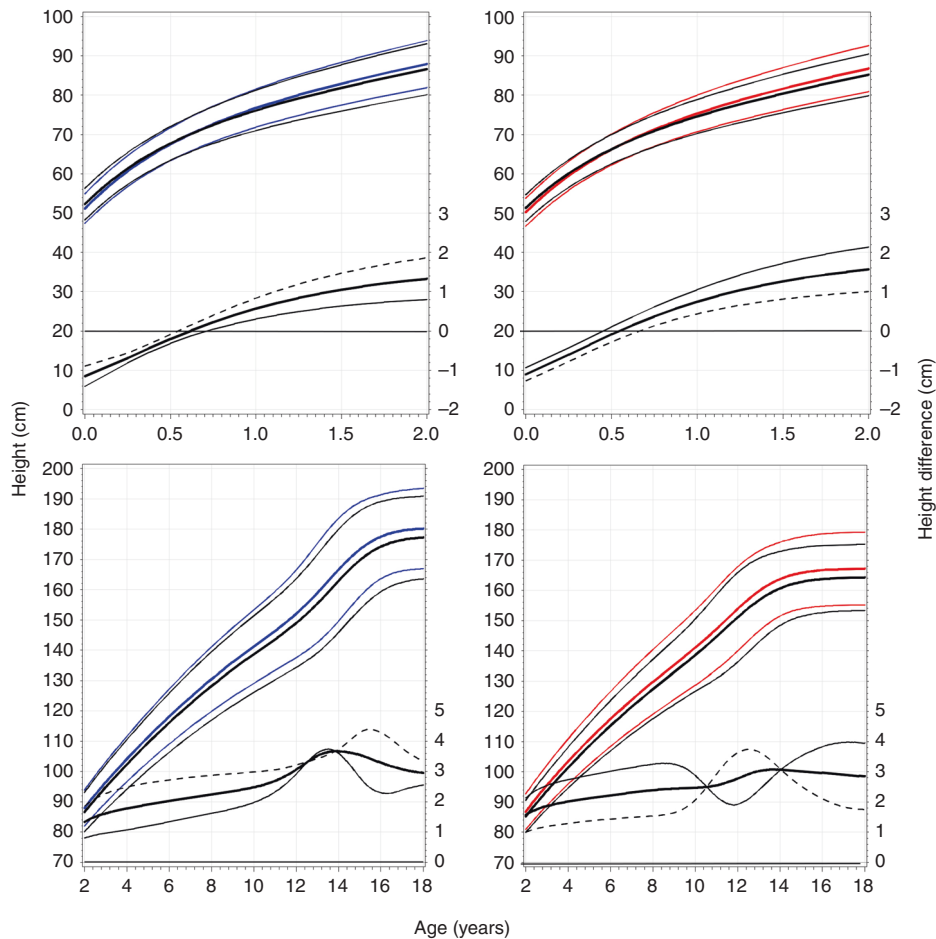


Fig. 4 Mean total height and difference in height of the Gothenburg 1974 and Edinburgh cohorts. Mean total height (upper part of each panel), and difference in height (bottom part of each panel) of the Gothenburg 1974 (blue/red) and Edinburgh cohorts (black). Boys to the left and girls to the right. Heights are visualized with ± 2 SDS (left-axis scale). A difference above the 0-line (right) indicates that the Gothenburg cohort is taller (right-axis scale).

cohorts born around 1974 and 1990.⁹ The multivariable analyses showed that the Q_{max} estimate explained most of the variation in attained adult height in both these study groups.

Adult height was nearly 3 cm shorter in the Edinburgh cohort for both sexes, a result of less prepubertal basic (i.e. QE -function) growth during infancy and childhood and not due to slower growth during the pubertal years. Using multivariable regression models, we were able to show that the contribution of the different growth functions explaining variations in adult height was similar in the two cohorts born in mid-1970s in north-western Europe. Q_{max} was the single estimate explaining most of the variation. As for almost all aspects of life, human growth is influenced by both nature and nurture, genes, and environment. In the 1970s, both Sweden and Scotland had been relatively homogeneous welfare states for several decades and both countries have reported a positive secular trend for childhood and adult heights during the second half of the twentieth century.^{7,38–40} The somewhat shorter heights during childhood, adolescence, and attained adult height in this Scottish cohort could be due to slightly less advantageous socio-economic situation compared with Sweden, but also due to genetic differences, or a combination of both. Despite the partly common genetic background from Indo-European tribes 5000–10,000 years ago and a possible influence by Scandinavian Vikings in Scotland 1300–1110 years ago, there are some genetic differences that could explain some of the differences in stature, at least for males. The Y haplogroup IM170 gene is common in South Western

Scandinavia and the Netherlands, regions with tall males, whereas the Y haplogroup R1b-S116 gene is most common in Portugal, Spain, Southern France, Ireland, and Scotland, regions with relatively shorter male stature.⁴¹

Strengths and limitations

A major strength of the present study was that it shows the QEPS model can be employed to analyze a dataset that differs in design from previous situations in which this model has been used. Another new finding was the CIs for estimated growth functions became very narrow and the average fit of the model was very accurate in a growth study with repeated semi-annual measurements such as the Edinburgh longitudinal growth study. The result noting the similarities in pubertal growth is confirmatory. Analysis of the pubertal growth pattern has been a major topic in previous studies using QEPS model.^{9,23,25,30,31}

One possible shortcoming was that QEPS was unable to characterize short-term changes as mini-fluctuations, seasonal variations, or any of the mid-childhood growth spurts in growth. This is on account of the model's rigid mathematical nature with four different growth functions and additional time-scale parameters. No other long-term growth model has been able to describe these short-time growth variations. For investigating short-term changes (within days) in longitudinal bone growth, the interval between the measurements needs to be very frequent, and thereby depending on a very precise measuring technique such as a knemometer or implanted tantalum bullets.^{42–46} For

Table 3. Comparison of growth characteristics for pubertal growth.

(A)	Gothenburg cohort, girls (n 1165)			Edinburgh cohort, girls (n 68)			Diff. ^a	P value
	Mean	SD	95% CI	Mean	SD	95% CI		
Age at 5% of the pubertal growth (years)	9.87	0.98	9.81–9.92	9.97	1.20	9.68–10.26	0.10	0.49
Age at peak height velocity (years)	11.84	0.98	11.79–11.90	11.92	1.21	11.63–12.21	–0.08	0.61
Age at 50% of the pubertal growth (years)	12.10	0.97	12.04–12.16	12.15	1.21	11.86–12.45	–0.05	0.67
Age at 95% of the pubertal growth (years)	14.67	0.97	14.62–14.73	14.67	1.23	14.37–14.97	–0.30	0.96
Height at 5% of the pubertal growth (cm)	139.44	6.96	139.04–139.84	137.21	6.35	135.67–138.75	2.23	0.010
Height at peak height velocity (cm)	152.38	6.19	152.02–152.73	149.95	5.66	148.58–151.32	2.43	0.0016
Max value of P-function (cm)	12.80	3.63	12.59–13.01	12.90	3.16	12.13–13.66	–0.10	0.83
Specific pubertal height gain ^b (cm)	11.52	3.27	11.33–11.71	11.61	2.85	10.92–12.30	–0.09	0.83
Pubertal QES gain ^b	14.85	2.52	14.70–14.99	14.19	2.85	13.50–14.88	0.66	0.040
Height gain during puberty ^b (cm)	26.37	3.83	26.15–26.59	25.80	3.68	24.91–26.69	0.57	0.24
Duration of pubertal growth ^b (years)	4.81	0.20	4.80–4.82	4.70	0.19	4.65–4.74	0.11	<0.0001
Tmax ^c (cm)	167.26	6.06	166.92–167.61	164.44	5.56	163.10–165.79	2.82	<0.0001
(B)	Gothenburg cohort, boys (n 1174)			Edinburgh cohort, boys (n 89)			Diff. ^a	P value
Variable	Mean	SD	95% CI	Mean	SD	95% CI		
Age at 5% of the pubertal growth (years)	11.82	0.97	11.76–11.87	11.98	0.93	11.78–12.17	–0.16	0.13
Age at peak height velocity (years)	13.69	0.97	13.64–13.75	13.86	0.96	13.66–14.06	–0.17	0.12
Age at 50% of the pubertal growth (years)	13.84	0.97	13.78–13.89	14.00	0.96	13.80–14.20	–0.16	0.12
Age at 95% of the pubertal growth (years)	16.13	0.98	16.08–16.19	16.30	1.01	16.09–16.52	–0.17	0.12
Height at 5% of the pubertal growth (cm)	149.89	7.04	149.49–150.29	147.96	6.87	146.51–149.40	1.93	0.013
Height at peak height velocity (cm)	163.86	6.61	163.48–164.24	161.52	6.62	160.12–162.91	2.34	0.001
Max value of P-function (cm)	17.38	3.64	17.18–17.59	16.98	3.40	16.26–17.69	0.40	0.31
Specific pubertal height gain ^b (cm)	15.65	3.27	15.46–15.83	15.28	3.06	14.63–15.92	0.37	0.31
Pubertal QES gain ^b	13.32	2.16	13.20–13.45	12.81	1.97	12.40–13.22	0.51	0.030
Height gain during puberty ^b (cm)	28.97	3.61	28.76–29.17	28.09	3.34	27.38–28.79	0.88	0.026
Duration of pubertal growth ^b (years)	4.32	0.21	4.31–4.33	4.33	0.27	4.27–4.38	–0.01	0.75
Tmax ^c (cm)	180.53	6.67	180.14–180.91	177.66	6.83	176.22–179.09	2.87	<0.0001

^aDifference between mean values.

^bPubertal growth as growth in cm from heights at 5 to 95% of the pubertal growth function.

^cTotal height, calculated adult height by QEPS model.

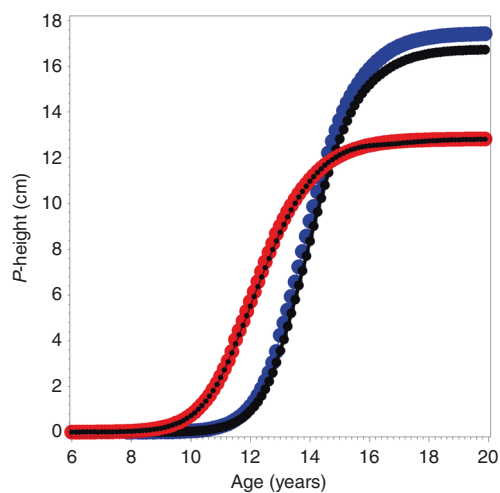


Fig. 5 QEPS pubertal height functions for Gothenburg and Edinburgh cohorts. QEPS Pubertal height functions (medians) for Gothenburg girls (red open circles) and Edinburgh girls (black dots), for Gothenburg boys (open blue circles) and for Edinburgh boys (black dots) in relation to chronological age.

identifying changes within growth phases, such as the mid-childhood growth spurts, measurements every 6 months were needed.^{27,28} On looking at *individual growth curves* calculated by QEPS, mid-childhood growth spurts may be seen as oscillations around the individual QEPS-growth curve, but they are relatively small and hard to distinguish from differences between measurers or to the influence of diurnal variation.^{19,20}

Usefulness of the QEPS growth model

The QEPS growth model, now externally validated for a more generalized use, will be a valuable tool for researchers studying different populations and patient groups with longitudinal growth measurements, as pioneered with pathologically obese patients.³¹ QEPS offers a detailed description of growth according to the different growth functions with CI for describing pathophysiology defined by values outside estimates of the QEPS references.^{22,23} The different growth functions in the QEPS growth model will also be a valuable tool for exploring regulation of growth of the different growth phases, as done for the GH-dependent childhood phase.⁴⁷ For the clinician, tools based on the QEPS model will in due course be available for monitoring longitudinal growth of any child for the purpose of predicting future growth. This will be possible, since the QEPS model calculates the individual growth curve from past measurements from birth onwards, from which

Table 4. Multivariable regression analyses explaining the contribution of *Q*, *E*, *P*, and *AgeP50* growth estimates to adult height.

Group	<i>E</i> _{max}	<i>Q</i> _{max}	<i>E</i> _{max} , <i>Q</i> _{max}	<i>E</i> _{max} , <i>Q</i> _{max} , <i>P</i> _{max}	<i>E</i> _{max} , <i>Q</i> _{max} , <i>P</i> _{max} , <i>AgeP50</i>
Girls Gothenburg	12.3	41.8	67.7	86.5	99.5
Girls Edinburgh	4.9	41.7	58.9	77.9	98.4
Boys Gothenburg	9.0	49.2	69.7	89.9	99.5
Boys Edinburgh	11.8	57.6	66.9	91.1	99.5

Explanation of variance in adult height by QEPS estimates (percentage).

the predicted future growth curve can be obtained. This will allow the observed future growth to be interpreted as expected or unexpected, and if abnormal the child investigated for underlying etiology, and adequate treatment given. However, this concept has since long been applied during GH treatment, where untreated QE-growth predicted and used for predicting the GH growth response.⁴⁷ Moreover, a novel type of references taking the broad variation in biological maturation into account was developed applying the QEPS growth model, overcoming the shortcoming of traditional chronological age reference.³⁰ Such puberty-adjusted growth references allow an improved, more sensitive, evaluation of growth at the individual level during adolescence.³⁰

CONCLUSION

The QEPS height model is now, for the first time validated in the Edinburgh growth study, a longitudinal study of healthy individuals with a different study design encompassing more evenly distributed measurements than in the GrowUp Gothenburg cohorts used in previous studies. We found that by having a large number of individual measurements within each growth phase, the QEPS-model calculates growth estimates with high precision as seen by narrow CI of the estimates and high accuracy as seen by the low values of the standard error of the fit. The two different growth cohorts born in the mid-1970s from Scotland and Western Sweden had remarkably similar growth patterns, especially in the puberty component where the timing and magnitude of growth was very similar between the cohorts for both sexes. Despite the Scottish study group being shorter as adults, the contribution of each growth function to the mean adult height and explaining the variation in adult height were similar in both cohorts. The validation of the QEPS model in this new study setting is an important step for further generalized use of the model answering different research questions and for improved monitoring and height prediction by the development of clinical tools for growth evaluation.

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AUTHOR CONTRIBUTIONS

All five authors developed the study concept and design. K.A.-W. and G.B. are principal investigators of the study populations used. A.F.M.N. performed the QEPS-analyses and made Fig. 2. A.N. made the other figures and performed the statistical analyses. A.H. made the tables and wrote the first draft of the paper. All five authors critically revised the paper for important intellectual content and approved the final manuscript to be submitted for publication.

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COMPETING INTERESTS

A.F.M.N. works for Muvara, Multivariate Analysis of Research Data, Statistical Consultation, the Netherlands. The authors declare no competing interests.

CONSENT STATEMENT

All study subjects and their parents or guardians gave informed written consent to participate in research studies as required by the local ethics committees.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41390-021-01790-2>.

Correspondence and requests for materials should be addressed to Anton Holmgren.

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