Insight into human pubertal growth by applying the QEPS growth model

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Abstract

Background: Computerized mathematical models describing absolute and relative individual growth during puberty in both cm and standard deviation (SD)-scores are lacking. The present study aimed to fill this gap, by applying the QEPS-model that delineates mathematically the specific pubertal functions of the total growth curve.

Methods: Study population used was the individual growth curves of the longitudinally followed cohort GrowUp1974 Gothenburg (n = 2280). The QEPS-model describes total height as a combination of four shape-invariant growth functions, modified by time-scale and height-scale parameters: a quadratic-function for the continuous growth from fetal life to adulthood; a negative exponential-function adds the rapid, declining fetal/infancy growth; a pubertal-function the specific pubertal growth spurt; a stop-function the declining growth until adult height. A constructed variable, MathSelect, was developed for assessing data-quality. CIs and SD-scores for growth estimates were calculated for each individual.

QEPS-model estimates used for pubertal growth; from the T-function: onset of puberty as minimal height velocity (AgeTONSET); mid-puberty as peak height velocity (AgeTPHV); end of puberty as height velocity decreased to 1 cm/year (AgeTEND); duration of different intervals and gain (AgeTONSET-END and Tpubgain); from the P-function: onset of puberty, estimated as growth at 1% or 5% (AgeP1,AgeP5); mid-puberty as 50% (AgeP50) and PHV (AgePPHV); end of pubertal growth at 95 or 99% (AgeP95, AgeP99); duration of different intervals and pubertal gain (Ppubgain; P max); from the QES-function: gain (QESpubgain).

Results: Application of these mathematical estimates for onset, middle and end of puberty of P-function, QES-function, and T-function during puberty showed: the later the onset of puberty, the greater the adult height; pubertal gain due to the P-function growth was independent of age at onset of puberty; boys had higher total gain during puberty due to P-function growth than to QES-function growth; for girls it was reversed.

Conclusions: QEPS is the first growth model to provide individualized estimates of both the specific pubertal growth function and the total growth during puberty, with accompanying SD-scores and CIs for each individual. These QEPS-derived estimates enable more in-depth analysis of different aspects of pubertal growth than previously possible.

Keywords: Puberty, Growth model, Onset of puberty, Peak height velocity, End of puberty, Duration of puberty, Data quality, Cumulative distribution, Confidence interval
Background

Pubertal growth is unique to humans [1]. For the individual, puberty constitutes a dramatic change in both the magnitude and tempo of growth. In a healthy population, there is wide variation in when children enter puberty, both within and between genders [2, 3]. Thus, accurately describing this period of growth is challenging due to the complexity of the changes that occur and the differences observed between individuals. At present, methods for modelling pubertal growth are limited, and no existing growth references allow appropriate adjustments for the onset of puberty. Furthermore, variations between individuals add to the challenges of modeling growth, particularly when they are considered to be related to maturation (biological age) rather than to chronological age. The pattern of pubertal growth has also changed over time, and varies between different populations [4, 5]. The large variations in both the timing of puberty and amount of growth which are apparent among individuals and between populations highlight the need for individualized equations and estimates describing pubertal growth.

The years preceding puberty are characterized by a period of slowly declining height velocity [3, 6]. The onset of pubertal growth can be identified based on the smallest height velocity that precedes what has been referred to as the take-off, onset, nadir or insertion point [2, 3, 7]. In previous studies it has also been described as the point at the beginning of the pubertal growth spurt where height increased by 0.3 standard deviation (SD) scores, or as the point 2 years before peak height velocity (PHV) [6, 8, 9]. Thereafter, height velocity rapidly increases, and the SD of both observed height and height velocity for any population increases due to the broad variation in the timing of puberty [3]. PHV – the mid-point in puberty where growth is most pronounced – has often been used as the only estimate of pubertal growth in previous research. The easiest, and probably most unreliable, way of defining age at PHV is by estimating the age at which height increases most from the growth curve, either by visual inspection or using a specific puberty ruler [10]. Age at PHV in contemporary research may also be defined by visual inspection of the change in growth velocity on a computer-generated height velocity chart [2, 11]. Another way of defining age at PHV is to take the age at the midpoint in the interval between the two height measurements with the greatest calculated yearly height increment [6, 12]. The latter is reliable when height measurements are available every 3 months, but less precise when measurements are taken at longer intervals; there is a risk of under-estimating the age at PHV when measurements are at 6- or 12-month intervals [9, 13]. The end of pubertal growth has typically not been specifically identified, and measurements have instead been based on when adult height was attained. Therefore, the total pubertal height gain has been defined as the amount of growth observed from the onset of pubertal growth until adult height, with the duration of pubertal growth defined as the time period from the onset of puberty to the attainment of adult height [2, 12, 14].

Few studies have attempted to describe the whole pattern of pubertal growth in a detailed manner, including separate estimations of growth for the onset, middle and end of the pubertal period. In 1980, Taranger & Hägg described a way to estimate the duration and gain of pubertal growth based on visual inspection of individual growth charts [15]. Mathematical models have also been used to describe growth from birth to adult height [16–19]. The ICP-model (Infancy-Childhood-Puberty), developed in Gothenburg by Karlberg et al, was the first model to use three different mathematical functions related to the periods of biological growth [12, 20, 21]. Thus, during the pubertal years, total growth can be separated into the childhood component and the pubertal component. However, the pubertal component of the ICP-model has a fixed form, such that only the timing of pubertal growth, not the magnitude of the specific pubertal growth function, can be individualized. This means that the model assumes that all variations in pubertal growth in individuals of the same gender are related to differences in the childhood growth component that is still ongoing during the pubertal period [21]. The first published growth model that allowed for individualization of the pubertal growth was the SITAR-model by Cole et al. [22]. The model generates a growth curve and three subject-specific parameters (size, tempo and velocity) that can be adjusted to describe individual growth patterns. However, this model cannot separate growth during puberty into different components, instead providing only one mean shape-invariant growth function.

The first model to describe individual longitudinal human growth and its different phases from fetal life until adult height is the QEPS-model by Nierop et al. [23]. The model was constructed with a combination of four distinct shape-invariant growth functions: Quadratic (Q), Exponential (E), Pubertal (P) and Stop (S), (Fig. 1). All four functions have an individual height-scale parameter, and the E- and P-functions also have individual time-scale parameters; giving six modifying parameters in total to describe individual growth. Basic features of the Q and E functions have been used in previous prediction models [24–26].

In the present study we implement novel estimates of pubertal growth from the QEPS mathematical growth model in cm and SD-scores both at the individual and the group level. The model calculates both the specific pubertal P-function during puberty and the from prepubertal period ongoing QES-functions, as well as the combined total growth. Moreover, the
model provides confidence intervals (CIs) of the different growth estimates that can be used to assess the quality of growth data at the individual level. Basic features of the QEPS-model have been presented at meetings [27–29].

Methods

Ethical approval

Ethical approval was obtained from the ethics committee of the University of Gothenburg (91–92/131–93), and individual approval was given by the participants of the 1974 cohort study if they were 18 years or older, or by their legal guardian if they were not old enough to give consent (16 to 18 years of age).

Subjects – A healthy cohort born in 1974

The data used for analysis was from a community-based, observational growth study the GrowUp1974 Gothenburg study that was conducted in all high schools in Gothenburg, Sweden in 1992 [3]. Longitudinal growth data from healthy individuals born at term (gestational age 37–42 weeks) within this study, together with data from the Swedish Medical Birth Registry, were used to create the Swedish national Growth References used from 2000 [3, 30]. A study group of individuals with longitudinal growth data was selected from the GrowUp1974 population for the present study using the following steps.

1. Computerized selection of individuals with height measurements registered for each of the following ages were selected: at birth; as an infant 0 to 9 months (two or more measurements); as a toddler between 9 months and 3.5 years; as a child 3.5 to <6.0 years; as a schoolchild; 6.0 to <9.0 years; as a juvenile 9.0 to <12.0 years; in adolescence 12.0 to <16.0 years; and in adulthood > = 16 years.

2. Visual growth curve analysis for confirmation of the growth characteristics of the individuals in the selected study group; see Growth curve analysis section below. This selection reduced the study group with 696 individuals from 2976 to 2280 individuals. The main characteristics of the study group are shown in Table 1.

![Fig. 1 The QEPS-model. Left panel: The total height (QEPS) is the sum of four growth functions: a quadratic growth function (Q), a negative exponential growth function (E), a pubertal growth function (P) and a stop function (S) modelling the end of growth for function Q. B = birth, t0 = about 6 weeks after conception. Birth is marked with a vertical line. Age scale below 3 years is stretched out. Right panel: QEPS model for total height, T(age) = E(age) + QS(age) + P(age), with QS(age) = Q(age) – S(age). Tmax = Emax + QSmax + Pmax AgeP5 and AgePS0 mark the ages where 5% and 50% of Pmax are reached, AgeS0 marks the age where the S-function is starting. Originally published in Journal of theoretical biology 2016;406:143–65, Nierop AF et al., used by permission of Elsevier journals](image-url)
Mathematical selection criterion (MathSelect)
To assess the quality of the fitted individual total height function, \(T(\text{age})\), a mathematical selection criterion, MathSelect, was used that we developed for the QEPS-model. The MathSelect criterion combines information from nine individual variables. Details on how MathSelect was constructed can be found in the Additional file 1: Section A2. Two different MathSelect values, 0.975 and 0.68 were used for computerized data quality check of the study group. For all figures MathSelect 0.975 was used.

Processing of the data
To construct a longitudinal growth curve for each individual in the present study group, data files were analysed with Matlab software (version 7.13.0 R2012b, The Mathworks). The Matlab Curve Fitting Toolbox was used for regular curve fitting and was customized to perform penalized curve fitting. Individual curves were estimated with 95% CIs for the fitted parameters.

Growth curve analysis
The quality of the height data were evaluated by visual inspection using QEPS-model-fitted growth charts. The quality of data, and the presence of potential errors that needed further assessment, were evaluated by stepwise observations:

1. Assessment of outliers; assessment of individual height data that deviated from the individual growth curve, giving rise to suspicion of input or measurement errors.
2. Assessment of the adult height; visual analysis of whether adult height was reached at the last measurement or not.
3. Comparison between the new mid-puberty parameter \(\text{AgeP}50\) and visually evaluated age at PHV (\(\text{AgePHV}\)).

If there was a difference of more than 0.66 years between \(\text{AgeP}50\) and \(\text{AgePHV}\), or if observations 1 and 2 above gave rise to uncertainty regarding any data points, the original growth data were reevaluated; if uncertainty remained, the individuals were excluded from the study.

QEPS variables describing pubertal growth
Estimates from the QEPS total curve have the prefix \(T(\text{Total})\), using the basic additive QEPS- model in which \(T(\text{age}) = Q(\text{age}) + E(\text{age}) + P(\text{age}) - S(\text{age})\) [23]. From the Total growth curve, onset of pubertal growth, \(\text{AgeT}_{\text{ONSET}}\) was calculated as the age at minimum height velocity (HV) of the total height function. Mid-puberty was calculated as the age at PHV from the total growth curve (\(\text{AgeT}_{\text{PHV}}\)) and end of puberty as the age at which HV had decreased to 1 cm/year (\(\text{AgeT}_{\text{END}}\)). The total gain in height (cm) during puberty (\(\text{Tpub}T\text{gain}\)) was based on growth during the time period \(\text{AgeT}_{\text{ONSET}}\) - \(\text{AgeT}_{\text{END}}\). The total gain in adult height due to the specific \(P\)-function is estimated by the QEPS-model as the maximum height of the \(P\)-function, \(P_{\text{max}}\) in cm (\(P_{\text{max}} = T_{\text{max}} - \text{QES}_{\text{max}}\)). Due to the specific form of the \(P\)-function, which is a quadratic, logistic function, \(P_{\text{max}}\) can be calculated without defining a specific duration of puberty. The \(P\)-function starts before \(\text{AgeT}_{\text{ONSET}}\) since the velocity of \(T\) will not increase until the velocity of the \(P\)-function increases more than the decreasing velocity of the QES-function. If the relative influence of \(P\)- and QES-functions during the pubertal time period needs to be calculated, an age point is needed for both QES- and \(P\)-functions. Thus, onset of pubertal growth can be estimated from the \(P\)-function as the age when 1% (\(\text{AgeP}1\)) or 5% (\(\text{AgeP}5\)) of the total \(P\)-function-estimated gain was reached. For mid-puberty, we calculated the age when 50% of the \(P\)-function gain was achieved, \(\text{AgeP}50\), and the age at PHV from the \(P\)-function growth curve, \(\text{AgeP}_{\text{PHV}}\). In order to identify the end of pubertal growth, we calculated the age when 95% (\(\text{AgeP}95\)) or 99% (\(\text{AgeP}99\)) of the specific pubertal gain was achieved, Fig. 2. The time from \(\text{AgeP}5\) to \(\text{AgeP}95\), as well as \(\text{AgeP}1\) to \(\text{AgeP}99\) and \(\text{AgeT}_{\text{ONSET}}\) to \(\text{AgeT}_{\text{END}}\) gives estimates for the duration of pubertal growth.

In general, pubertal gain can be described as the increase in height of the \(T\), \(P\) and QES-function from \(\text{AgeT}_{\text{ONSET}}\) until \(\text{AgeT}_{\text{END}}\), and corresponding decomposition of the total puberty gain in a \(P\) and a QES part: \(T\text{gain} = P\text{gain} + \text{QESgain}\). The value of onset and end of pubertal growth can be any selected combination of onset of puberty age, expressed as \(\text{AgeT}_{\text{ONSET}}\) \(\text{AgeP}1\) or \(\text{AgeP}5\), with any selected end of puberty age, expressed as \(\text{AgeT}_{\text{END}}\) \(\text{AgeP}95\) or \(\text{AgeP}99\). During the selected pubertal period the model can separate the influence of the specific \(P\)-function from the ongoing \(Q\)-function, and also their relationship as a ratio with the locations of \(\text{AgeT}_{\text{ONSET}}\) and \(\text{AgeT}_{\text{PHV}}\); see Additional file 1: Section A1.3 for more information. Examples of pubertal growth for four individuals are shown adjusted for age at onset of puberty in Fig. 3, and their entire growth according to chronological age in Additional file 1: Figure S1, where the total pubertal growth is expressed in both cm and SD-scores, and is also divided into the \(P\)- and QES-functions. The details of the equations describing pubertal growth can be found in Nierop et al. [23], with complementary information explaining the pubertal period in more detail in the Additional files 1: Section A1.

Statistical considerations
The measured and calculated variables in the tables are presented as mean, median, standard deviation, maximum and minimum. Lower and upper 95% CIs, skewness and kurtosis computations conducted in order to estimate any departure from the normal distribution are
given in the Additional file 1: Tables. These computations were performed using SAS Software 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Pubertal growth estimates

The different pubertal growth estimates are shown in Tables 2 and 3, and in more detail in the Additional file 1: Tables S1 and S2. Differences in the mean between various pubertal estimates are shown below; grouped by the type of measurement; for pubertal duration and pubertal height results are given with the ±1 SD interval of the population in brackets.

Onset of pubertal growth

Estimates of timing for onset of pubertal growth vary depending on the variable used. For girls, the mean age at onset of puberty as AgeTONSET from the total growth curve was 9.24 years, 0.53 years after AgeP1 and 0.62 years before AgePS from the P-function. For boys, there was no difference between AgeTONSET (10.74) and AgeP1 (10.73), whereas AgePS occurred 1.0 years later, Table 2.

The median percentage of the P-function reached at the AgeTONSET was 2.4% for girls and 1% for boys, Additional file 1: Figure S2.

Mid-pubertal growth estimates

The visually estimated age at PHV (AgePHV) was compared with the QEPS-calculated AgeTPHV from the T-function and with AgeP50 from the P-function; the mean values of these four estimates of mid-pubertal growth showed minor differences from each other (maximal 3 months), Table 2. The difference in years between AgePHV and AgeP50 was −0.171 (±0.46 SD) for girls and 0.037 (±0.36 SD) for boys, Table 2. The median percentage of the P-function reached at mid puberty as AgeTPHV was 43% for girls and 45% for boys, Additional file 1: Figure S2, middle panel.

End of pubertal growth

For girls, the mean difference in years between AgeTEND from the total curve and AgeP95 from the P-function was 0.35, and the difference between AgeTEND and AgeP99 was −1.32. For boys, the corresponding values were 0.58 and −0.88 years, respectively, Table 2. For both genders, taller adult heights were found in individuals with later pubertal growth (later AgeP50); however, there was broad individual variation and apparent differences in the distribution of pubertal timing between genders, as seen in Fig. 4. When relating adult height to age at onset of puberty, the pattern was similar for both genders, see Additional file 1: Figure S4; a 1-year delay in
the onset of puberty, expressed as \( \text{Age}_{\text{TONSET}} \), will give an adult height that is taller by 1.2 cm in girls and 0.8 cm in boys. The percentage of \( P \)-function growth reached at \( S_0 \) was for girls 74% and for boys 89%, whereas at \( \text{Age}_{\text{TEND}} \) it was 97% for both genders. Additional file 1: Figure S2 right panel.

**Duration of pubertal growth**

For girls, the mean duration in years for pubertal growth from \( \text{AgeP5} \) to \( \text{AgeP95} \) was 4.80 (4.59–5.01), the duration from \( \text{AgeP1} \) to \( \text{Age99} \) was 7.61 (7.28–7.94) and the duration from the total growth curves defined as \( \text{Age}_{\text{TONSET-END}} \) was 5.77 (5.27–6.27).

The corresponding durations of pubertal growth in years for boys were 4.32 (4.10–4.54), 6.83 (6.49–7.17), and 5.94 (5.56–6.32), respectively, Table 2. A clear gender difference was seen in both timing and duration of pubertal growth when estimates were based on the \( P \)-function, Fig. 5, left panel, with not only a later, but also a shorter pubertal growth spurt seen in boys. This is in contrast to the less pronounced gender difference observed when the duration of pubertal growth was based on the total growth curve for the same age-points, Fig. 5, right panel.

**Gain of pubertal growth**

From the total growth curve, the mean pubertal gain for girls from \( \text{AgeP5} \) to \( \text{Age95} \) was 26.34 cm (18.74–33.94), and from \( \text{AgeP1} \) to \( \text{Age99} \) it was 33.64 cm (24.52–42.76). For boys, the corresponding pubertal
The pubertal gain can also be described as what the specific P-function adds to the ongoing QES-function. The mean pubertal gain, from the P-function, $P_{\text{max}}$, was 12.73 cm for girls and 17.34 cm for boys, and was not influenced by the timing of puberty, as seen in Fig. 6, upper left panel (with $P_{\text{pubgain}}$, 95% of $P_{\text{max}}$). However, for both genders, the increase in total height during the pubertal years, $T_{\text{pubgain}}$, appeared to be higher for individuals with earlier puberty compared with those with later puberty, due to differences in the growth from the

Table 2  Age in years for pubertal growth estimates

| Variable                              | N  | Mean  | Median | SD   | Max  | Min  |
|---------------------------------------|----|-------|--------|------|------|------|
| **Girls:**                            |    |       |        |      |      |      |
| Onset of puberty                      |    |       |        |      |      |      |
| AgeTonset, age at minimum height velocity of the T-function$^a$ | 1129 | 9.24  | 9.19   | 1.01 | 12.62| 6.37 |
| AgeP1, age at 1% of the P-function$^b$ | 1139 | 8.71  | 8.68   | 0.98 | 12.00| 6.09 |
| AgeP5, age at 5% of the P-function    | 1139 | 9.86  | 9.81   | 0.97 | 13.13| 7.30 |
| Mid puberty                           |    |       |        |      |      |      |
| AgePHV, age at visual estimated PHV   | 1134 | 11.92 | 11.88  | 0.97 | 15.31| 9.35 |
| AgeTPHV, age at PHV of the T-function| 1129 | 11.83 | 11.80  | 0.96 | 15.09| 9.39 |
| AgePPHV, age at PHV of the P-function| 1139 | 12.02 | 11.98  | 0.95 | 15.26| 9.51 |
| AgeP50, age at 50% of the P-function  | 1139 | 12.09 | 12.06  | 0.95 | 15.34| 9.59 |
| End of puberty                        |    |       |        |      |      |      |
| AgeP95, age at 95% of the P-function  | 1139 | 14.66 | 14.65  | 0.95 | 17.93| 12.23|
| AgeP99, age at 99% of the P-function  | 1139 | 16.33 | 16.34  | 0.95 | 19.63| 13.91|
| AgeTend, age where the height velocity has decreased to 1 cm/year | 1139 | 15.01 | 15.03  | 0.84 | 18.00| 12.85|
| Duration                              |    |       |        |      |      |      |
| Duration between AgeP5 and AgeP95    | 1139 | 4.80  | 4.78   | 0.21 | 5.54 | 3.44 |
| Duration between AgeP1 and AgeP99    | 1139 | 7.61  | 7.58   | 0.33 | 8.77 | 5.45 |
| Duration between Tonset and Tend      | 1129 | 5.77  | 5.78   | 0.50 | 7.11 | 3.84 |
| **Boys:**                             |    |       |        |      |      |      |
| Onset of puberty                      |    |       |        |      |      |      |
| AgeTonset, age at minimum height velocity of the T-function$^a$ | 1141 | 10.74 | 10.71  | 0.98 | 14.20| 7.50 |
| AgeP1, age at 1% of the P-function$^b$ | 1141 | 10.73 | 10.72  | 0.97 | 13.94| 7.45 |
| AgeP5, age at 5% of the P-function    | 1141 | 11.78 | 11.77  | 0.96 | 14.98| 8.56 |
| Mid puberty                           |    |       |        |      |      |      |
| AgePHV, age at visual estimated PHV   | 1136 | 13.83 | 13.81  | 1.00 | 17.18| 10.95|
| AgeTPHV, age at PHV of the T-function| 1141 | 13.66 | 13.65  | 0.96 | 16.84| 10.54|
| AgePPHV, age at PHV of the P-function| 1141 | 13.73 | 13.72  | 0.96 | 16.94| 10.63|
| AgeP50, age at 50% of the P-function  | 1141 | 13.80 | 13.78  | 0.96 | 17.01| 10.69|
| End of puberty                        |    |       |        |      |      |      |
| AgeP95, age at 95% of the P-function  | 1141 | 16.10 | 16.06  | 0.97 | 19.31| 13.12|
| AgeP99, age at 99% of the P-function  | 1141 | 17.56 | 17.52  | 0.98 | 20.78| 14.58|
| AgeTend, age where the height velocity has decreased to 1 cm/year | 1141 | 16.68 | 16.64  | 0.90 | 19.44| 14.01|
| Duration                              |    |       |        |      |      |      |
| Duration between AgeP5 and AgeP95    | 1141 | 4.32  | 4.31   | 0.22 | 5.55 | 3.24 |
| Duration between AgeP1 and AgeP99    | 1141 | 6.83  | 6.82   | 0.34 | 8.78 | 5.12 |
| Duration between Tonset and Tend      | 1141 | 5.94  | 5.94   | 0.38 | 7.62 | 4.37 |

$^a$Total height function in cm; $T(\text{age}) = Q(\text{age}) + E(\text{age}) + P(\text{age}) - S(\text{age})$.

$^b$Quadratic logistic function describing the pubertal growth spurt $P(\text{age})$ in cm.

Gains were 29.00 (21.72–36.28) and 35.62 cm (27.10–44.14), respectively, Table 3.
QES-function during these years, Fig. 6, upper middle-right panels. The \( P_{\text{pubgain}} \) was clearly negatively related to \( Q_{\text{max}} \), the higher the \( Q_{\text{max}} \), the lesser the \( P_{\text{pubgain}} \), also the \( T_{\text{pubgain}} \) was negatively correlated to \( Q_{\text{max}} \), but to a lesser extent as seen in Fig. 6, lower panels.

Using the QEPS-model, pubertal gain can also be shown for each individual both as total gain and divided into the individual components of the \( P \)-function and the ongoing QES-function, Fig. 2, left. For the whole study population during the pubertal years, defined as the time period \( \text{AgeP5}–100 \) in Fig. 7, growth from the QES-function dominated in girls, whereas growth from the \( P \)-function dominated in boys, but with large inter-individual variations for both genders.

### Table 3 Estimated heights and pubertal gains in cm

| Height at Tonset, age at minimum height velocity of the T-function\(^a\) | N  | Mean | Median | SD  | Max  | Min  |
|-----------------------------|----|------|--------|-----|------|------|
| Girls:                      |    |      |        |     |      |      |
| Onset of puberty            |    |      |        |     |      |      |
| Height at AgeP1, age at 1% of the P-function\(^b\) | 1139 | 133.34 | 133.34 | 7.09 | 155.41 | 110.94 |
| Height at AgeP5, age at 5% of the P-function | 1139 | 139.47 | 139.36 | 6.91 | 160.72 | 116.45 |
| Mid puberty                 |    |      |        |     |      |      |
| Height at AgeTPHV, PHV of the T-function | 1129 | 152.37 | 152.32 | 6.15 | 169.62 | 130.45 |
| Height at P50, age at 50% of the P-function | 1139 | 154.29 | 154.07 | 6.25 | 171.68 | 131.92 |
| End of puberty              |    |      |        |     |      |      |
| Height at AgeP95, age at 95% of the P-function | 1139 | 165.81 | 165.77 | 6.04 | 181.91 | 144.26 |
| Height at AgeP99, age at 99% of the P-function | 1139 | 166.98 | 167.02 | 6.04 | 183.09 | 145.41 |
| Height at Tend, age where the height velocity has decreased to 1 cm/year | 1139 | 166.24 | 166.24 | 6.05 | 182.39 | 144.65 |
| Adult height (AH)           | 1139 | 167.66 | 167.6  | 6.06 | 183.7  | 146.5  |
| Height gain                 |    |      |        |     |      |      |
| Growth in height between AgeP5 and AgeP95 | 1139 | 26.34 | 26.35  | 3.81 | 37.86 | 12.98 |
| Growth in height between AgeP1 and AgeP99 | 1139 | 33.64 | 33.57  | 4.56 | 47.33 | 18.62 |
| Growth in height between Tonset and Tend | 1129 | 30.09 | 30.14  | 5.18 | 45.56 | 11.79 |
| Growth in height between Tonset and AH | 1129 | 31.51 | 31.54  | 5.34 | 46.86 | 12.73 |
| Boys:                       |    |      |        |     |      |      |
| Onset of puberty            |    |      |        |     |      |      |
| Height at Tonset, age at minimum height velocity of the T-function | 1141 | 144.60 | 144.28 | 7.45 | 168.17 | 116.45 |
| Height at AgeP1, age at 1% of the P-function | 1141 | 144.53 | 144.17 | 7.03 | 166.56 | 117.83 |
| Height at AgeP5, age at 5% of the P-function | 1141 | 149.76 | 149.36 | 6.97 | 170.80 | 122.56 |
| Mid puberty                 |    |      |        |     |      |      |
| Height at AgeTPHV, PHV of the T-function | 1141 | 163.74 | 163.40 | 6.54 | 182.12 | 138.82 |
| Height at P50, age at 50% of the P-function | 1141 | 165.03 | 164.67 | 6.58 | 183.59 | 140.06 |
| End of puberty              |    |      |        |     |      |      |
| Height at AgeP95, age at 95% of the P-function | 1141 | 178.75 | 178.50 | 6.59 | 199.06 | 155.64 |
| Height at AgeP99, age at 99% of the P-function | 1141 | 180.15 | 179.85 | 6.62 | 200.77 | 157.01 |
| Height at Tend, age where the height velocity has decreased to 1 cm/year | 1141 | 179.62 | 179.35 | 6.62 | 200.29 | 156.49 |
| Adult height (AH)           | 1141 | 180.69 | 180.4  | 6.63 | 201.7  | 157.3  |
| Height gain                 |    |      |        |     |      |      |
| Growth in height between AgeP5 and AgeP95 | 1141 | 29.00 | 28.97  | 3.64 | 40.17 | 16.68 |
| Growth in height between AgeP1 and AgeP99 | 1141 | 35.62 | 35.55  | 4.26 | 49.39 | 22.17 |
| Growth in height between Tonset and Tend | 1141 | 35.02 | 35.08  | 4.74 | 48.61 | 16.41 |
| Growth in height between Tonset and AH | 1141 | 36.09 | 36.10  | 4.89 | 51.39 | 17.16 |

\(^a\)Total height function in cm; \( T(\text{age}) = Q(\text{age}) + E(\text{age}) + P(\text{age}) - S(\text{age}) \).

\(^b\)Quadratic logistic function describing the pubertal growth spurt \( P(\text{age}) \) in cm.

\(^c\)Peak height velocity
tempo-adjusted SD-scores for pubertal age and height
The QEPS-model calculates the age of the individual for all pubertal estimates, which enables these estimates to be compared with the mean of the background population as relative age in deviations from the mean (i.e. standardized age in SD-scores). Thus, instead of showing the age of a child in chronological age, the age at onset of puberty can be visualized according to the mean age (zero) of the internal reference for onset of puberty, i.e. adjusted to pubertal age [23]. With this tempo-correction for the onset of puberty, the QEPS-model enables an individualized reference of pubertal growth in which heightSDS can be expressed according to a pubertal tempo-adjusted reference curve as shown in Fig. 3.

Moreover, in the examples of individuals presented in Fig. 3 and in the Additional file 1: Figure S1, (also presenting entire growth vs chronological age), the individual estimates of the different growth functions are presented not only in cm but also in individualized SD-scores.

In Fig. 8, we show the relationship between the mid-puberty variable, AgeP50, and its corresponding CI for standardized mid-puberty (AgeP50SDS). The scatterplot illustrates that the CI increases in those with later pubertal growth, especially in girls. Thus, there is a greater uncertainty in the estimate of mid-puberty for individuals with later pubertal growth.

Individual CIs for precision and MathSelect for quality assurance
From the whole study group, only 49 individuals were removed from the study population/analysis when using MathSelect < 0.975, and the absolute differences in pubertal population estimates were small. Kurtosis and skewness decreased only slightly in the MathSelect < 0.975 group (excluding CI estimates). In contrast, using MathSelect < 0.68, the study group was reduced by 731 individuals, and mostly by affecting skewness estimates, Additional file 1: Tables S3A–C.

There was a clear gender difference with higher CIs for girls for all QEPS variables for the onset, middle and end of pubertal growth.

Fig. 4 Scatterplot showing the relationship between adult height and AgeP50. Age at 50% of the P-function (AgeP50) for girls (red circles) and boys (blue crosses) in the study population is related to adult height. For girls; adult height = 152.707 + 1.204 x AgeP50, adjusted \( r^2 = 0.0363 \) (i.e. a 1-year delay in onset of puberty will give 1.20 cm taller adult height). For boys; adult height = 168.392 + 0.878 x AgeP50, adjusted \( r^2 = 0.0154 \) (i.e. a 1-year delay in onset of puberty will give 0.88 cm taller adult height).

Fig. 5 Scatterplot showing the relationship between the duration of pubertal growth and AgeP50. Left panel: Age from 5% of the pubertal growth (AgeP5) to age at 95% of the pubertal growth (AgeP95) for girls (red circles) and boys (blue crosses) in the study population, represents one estimate for duration of pubertal growth and is related to the timing of AgeP50. For girls; AgeP5 to AgeP95 = 5.030 – 0.0184 x AgeP50, adjusted \( r^2 = 0.0068 \). For boys; AgeP5 to AgeP95 = 4.246 + 0.0052 x AgeP50, adjusted \( r^2 = -0.0003 \). Right panel: Age from the minimum height velocity before pubertal growth spurt (AgeTONSET) to the age where the height velocity has decreased to 1 cm/year (AgeTEND) girls (red circles) and boys (blue crosses) represents one estimate for duration of pubertal growth and is related to the timing of AgeP50. For girls; AgeTONSET-END = 7.544 – 0.147 x AgeP50, adjusted \( r^2 = 0.081 \). For boys; AgeTONSET-END = 6.789 – 0.0616 x AgeP50, adjusted \( r^2 = 0.0244 \).
pubertal growth. Moreover, for both genders, the CIs for variables of onset and end of pubertal growth were broader, than for the estimates of mid-pubertal growth. Additional file 1: Tables S3A–C. These tables also show the resulting lower CIs when reducing the group by using the MathSelect function. The relationship between the CIs for AgeP50 and the MathSelect values is shown in Fig. 9. As expected from the modelling procedure, a lower MathSelect value corresponds to a lower maximum CI, whereas a higher maximum CI corresponds to a higher MathSelect value.

The relationship between the CI for AgeP50 and the P-function height gain (P_{\text{max}}) showed a nonlinear correlation; higher CIs were associated with lower P_{\text{max}}. Fig. 10. Independent of gender, a pubertal gain below 8 cm, gave a CI of more than 9 months, whereas a gain of at least 14 cm, gave a CI of less than 6 months as shown in Fig. 10. The apparent gender difference was related to the fact that a low P_{\text{max}} was more common in girls.

Additional file 1: Figure S4 shows a QEPS-calculated height velocity graph of an individual with low pubertal height gain, which further illustrates the problems in defining AgeT_{\text{PHY}} and AgeT_{\text{ONSET}} when the P-function is low. To be distinguishable, P_{\text{max}} must be greater than 50% of the CI, which for boys corresponds to a P_{\text{max}} of 2.74 cm and for girls to a P_{\text{max}} of 3.14 cm as seen in Additional file 1: Figure S5.

**Discussion**

**Principal findings: QEPS variables for pubertal growth enable new information**

The present study, as the first implementation of the QEPS-model to describe pubertal growth, describes the pubertal growth variables generated by the model and
their accompanying SD-scores for the population and the individual. Furthermore, the study demonstrates the potential to use these variables to explore human pubertal growth in greater detail than has previously been possible. The variables were calculated for the total growth curve during the pubertal years, and were also separated to provide information on growth specific to puberty, the P-function ($P_{pubgain}$), and growth related to the still ongoing QES-function ($QES_{pubgain}$). The $P_{pubgain}$ was found to be independent of age at onset of puberty, whereas the total height gain during puberty, also depending on the QES-function, was greater in those with earlier puberty. Moreover, a gender difference was identified, with more QES-function growth in girls and more P-function growth in boys.

As well as providing robust variables, the QEPS-model is the first growth model to provide individual CIs. Moreover, it allows height SD-score estimations during puberty to be expressed in relation to an individualized tempo-adjusted reference. This is a major achievement as it allows relative growth during the pubertal years to be expressed at any time-point; previous models have only been able to present total pubertal gain from prepuberty to adult height which has limited in depth analysis regarding pubertal growth [8]. By applying the QEPS-model to longitudinal growth data, we have identified new mathematical variables that are linked to specific time-points and which can be used to describe pubertal growth in detail, thus enabling comparison of growth patterns between individuals and populations. A practical advantage of using the QEPS-model compared to other growth models is that it automatically describes a wide variety of growth-related variables without relying on visual inspection of growth data; thus, the model is not subject to the estimation errors that can occur when relying on visual assessments.

**Onset of puberty**

The QEPS-model gives different time-points that differ from each other for onset of puberty; from the total growth curve as well as from the specific pubertal growth curve. Based on the specific P-function, ($AgeP1$), the onset of puberty was estimated to be 1.4 years earlier than in previous studies of pubertal growth in Scandinavian populations. Similarly, the onset of puberty was 0.9 years earlier when estimated based on the total growth curve, $Age_{ONSET}$ [2, 31]. Our findings are consistent with other studies using mathematical models [17, 19, 32], which typically result in earlier estimates of pubertal onset compared with studies using visual
estimates of the onset of puberty [13]. Future studies may show how the AgeP1 and AgeT_{ONSET} estimates correlate in the individual with the time when gonadal steroids start to increase during the nighttime [33, 34] which is another way of identifying onset of puberty. In fact, AgeP5 (9.9 years) at onset of puberty in girls is approximately equal to the onset of puberty in other Scandinavian studies; our results were only 0.24 years earlier than in the Finnish study [31] and 0.34 years earlier than in the Danish study [2], both of which used a visually defined onset of puberty. For boys, a consistency between AgeP5 (11.8) and onset of puberty in other Scandinavian studies was even greater than for girls, with differences varying from −0.18 to +0.24 years [2, 31, 35].

Mid-pubertal growth estimates
Mid-puberty, expressed as visual PHV, has so far been the main estimate of pubertal timing used in the literature [2, 6, 7, 17–19, 21, 31]. Here we compared three new estimates of mid-pubertal growth generated by the QEPS-model; from the total growth curve AgeTPHV, and from the P-function growth curve AgeP PHV and AgeP50, and found their mean values to be close to each other; both of the QEPS mathematically calculated variables of age at PHV were similar to visual age at PHV. For both boys and girls, we found the strongest correlation to be between AgeP50 and visual age at PHV [3]; at a population level, the mean difference between AgeP50 and visual PHV for boys was only 13 days and for girls 62 days. This suggests AgeP50 to be a variable that could be considered for use to identify age at mid-puberty in future studies of pubertal growth.

End of puberty and duration of pubertal growth
The QEPS-model enables us to estimate the end of pubertal growth. In fact, there is no other growth model today that can precisely estimate the end of growth [12, 17–19, 21, 22]; therefore, little attention has been paid to the end of pubertal growth. In this work, we introduced 95 and 99% of the P-function height gain (P\text{max}) for girls (red circles) and boys (blue crosses) in the study population is shown. For girls; AgePS0 = 1.445–0.1105 x P_{\text{max}} + 0.00290 x P_{\text{max}}^{2}, adjusted r^{2} = 0.4147. For boys; AgePS0 = 1.278–0.0800 x P_{\text{max}} + 0.00171 x P_{\text{max}}^{2}, adjusted r^{2} = 0.2890

Total pubertal gain
The shape-invariant QEPS-model is the first growth model that can calculate and describe the specific pubertal height
gain together with the total height gain during puberty at an individual level. The specific pubertal height gain was found to be independent of the age at onset of puberty. This was in contrast to the total height gain during the pubertal years which was greatest in those with an early onset of puberty, as reflected in the model by more growth associated with the QES-function than the P-function. It has been debated whether or not adult height is dependent on the timing of puberty [13, 36, 37]. The results of the present study confirm that there is an impact of a delay in onset of puberty, with a taller adult height in both boys and girls who experienced a later onset of puberty and a later AgeP50; in fact a 1-year delay gave approximately a 1 cm greater adult height. For some individuals, mainly girls, the estimated pubertal gain was so low that it was not possible to calculate either AgeTRHV or AgeTONSET from the total growth curve. We can now also define the specific component of the pubertal growth spurt, and using CIs we are also able to assess the accuracy of the estimated measurements. This represents an advance on what was possible using the previous ICP- and SITAR-models [12, 21, 22]. The relation between Ppubgain and QESpubgain varies between genders, but also between individuals, with more QESpubgain in those with earlier puberty.

**Tempo-adjusted individualized reference gives SD-scores for pubertal growth**

The relative age at onset of puberty is of major interest to both researchers and clinicians because of the great variation between individuals in biological maturity during the pubertal years [6]. So far, only changes in total pubertal height gain have been described with SD-scores. For the analysis of individual growth patterns during puberty, Tanner et al. constructed “tempo-conditional” height-velocity curves [6], for individuals with early, average or late puberty, which were applied and further modified in recently updated growth charts for the UK [38], whereas Karlberg superimposed pubertal growth curves adjusted for the timing of the mean age of PHV [12]. In the present study, we describe the individual pubertal growth curve in relation to a pubertal reference adjusted to both time and to age. We calculate and present numerically the relative pubertal age for each individual in comparison to the mean for the population reference curve, presented as SD-scores. Up to now, only the shape-invariant SITAR-model can adjust for individual tempo, amplitude, and size of total pubertal growth [22]. It is important to note that in contrast to the SITAR-model which only describes growth during the pubertal years, the QEPS-model can describe growth from birth until adult height, where growth during the pubertal years is based on two different additive functions that separate growth from the continuously ongoing QES-function from growth by the specific P-function. These different growth-functions are probably regulated by different factors/hormones, and will therefore be of considerable use when searching for/identifying regulatory factors for growth. Thus, these QEPS-variables will enable us to make a more precise description of individual growth during puberty, related to the individual timing of puberty, as well as to the balance between the different growth functions of the model. However, not only pubertal, but also good prepubertal data is required for calculating the QES-function as well as the P-function with good accuracy. Height expressed in SD-scores versus a tempo-adjusted height reference will serve as an individualized reference that is unique for this model.

**Quality markers of individual and population growth data**

Using CIs as a quality marker for growth in an individual has to our knowledge not been done before, despite the almost universal use of CIs to show the quality of data. Information on CIs makes it possible to visualize the quality of data for each individual; thereby providing information on the number of measurements that are required during the different periods of growth for the construction of a reliable growth curve at the individual level.

On the population level, data quality estimation by MathSelect enables the quality of growth data to be graded, and selection with the MathSelect function is easy and reproducible. We found it to be a useful instrument for identifying individuals with missing or unreliable height values; findings that were confirmed by visual inspection of the computerized growth charts of these individuals. Thus, using the MathSelect function can be a method for checking the quality of pubertal growth data in future studies, especially when it comes to the assessment of outliers and individuals for whom there may be measurement/input errors.

**Limitations of the study**

The current study presents results on pubertal growth that are specific for the population studied. Thus, the exact numerical values of the different pubertal variables cannot be generalized to pubertal growth in children born in other countries or during other times, with different tempo of secular changes. Instead, it can be used as a baseline for comparisons with studies in the future using either old or new data.

The implementation of the QEPS-model in this study was based on the same study group as the development of the model [3, 30], which may also be regarded as a limitation. However, the model was developed based on mean values, whereas in this present study, the implementation and analyses were done at an individual level, for the 2280 individuals included.

As a model for puberty, it is also important to note that the QEPS-model relies only on information about growth, without any information on the hormonal
changes and/or other manifestations that characterise this period of development. Future studies in individuals should be undertaken in order to correlate the pubertal growth variables from the QEPS-model with both hormonal changes \[33, 34, 39, 40\] and secondary sexual characteristics \[41–43\] in order to link the four growth functions with underlying biological processes.

**Conclusion**

During puberty, the QEPS-model can mathematically delineate the total growth curve as well as identify growth resulting from both the specific pubertal growth P-function and the continuation of the prepubertal growth QES-function, using four shape-invariant growth functions, with four height-scale and two time-scale parameters. Different variables estimating the onset, middle and end of pubertal growth will enable us to collect measures of both the duration of, and height gain associated with, the P-function in relation to total growth during puberty. The QEPS-model is the first growth-model that expresses the timing and amount of pubertal growth in individual SD-scores, thereby indicating both the tempo and the amount of growth at any time-point for the individual in relation to a reference population. Moreover, all pubertal variables are described with individual CIs for the first time, allowing both the population and individual measurements to be more precisely evaluated.

New insights have been achieved for gender-specific pubertal growth; the specific pubertal height gain was found to be independent of age at onset of puberty, whereas the total height gain during puberty, also depending on the QES-function, was greater in those with earlier puberty. Moreover, a gender difference was identified, with more QES-function growth in girls than boys and more P-function growth in boys than girls. The pubertal growth variables from the QEPS-model implemented in this study, will enable us to standardize methods to assess, describe and compare pubertal growth in different populations and patient sub-groups, and will also serve as a tool for gaining new insights into pubertal growth.

**Additional file**

Additional file 1: The first two sections explain pubertal variables of the QEPS-model in more detail in texts, figures and tables for the general pubertal growth, section A.1.1 and the individual variation in pubertal growth, section A.1.2, and the PQ variables in A.1.3. The construction of the mathematical selection criterion, MathSelect, is described in section A.2.1, in texts, figures and tables, and extreme possible values of the nine input variables corresponding with MathSelect values are computed in section A.2.2. (ZIP 4423 kb)

**Abbreviations**

AgeP1: age at which 1% of the P-function growth is reached; AgeP5: age at which 5% of the P-function growth is reached; AgeP50: age at which 50% of the P-function growth is reached; AgeP95: age at which 95% of the P-function growth is reached; AgeP99: age at which 99% of the P-function growth is reached; AgeFHV: visually estimated age at peak height velocity; AgeTEND: age at the end of puberty where the velocity has decreased to 1 cm/y for function T(age); AgeTTONSET: age at minimum height velocity of the T-function at start of the pubertal growth; AgeTEND: age at Peak Height Velocity of the T-function; CDF: cumulative distribution function; CI: confidence interval; E: negative exponential growth function of age E(age) in cm; Eorigin: individual time scale ratio, modifying the time scale of the E-function growth, with Eorigin = E(age) / mEmax; Emax gain in adult height in cm due to E-function growth; Eorigin: individual time scale ratio, modifying the time scale of the E-function growth, and therefore inversely related to the tempo of E. The origin is at e0, the age when length is theoretically zero, E(0) = 0; Q(max) = 0; HA: height acceleration; HeightSDS: Height position related to the reference standard deviation score; HV: height velocity; MaxCDF: individual maximum cumulative probability out of nine MathSelect step one cumulative distribution functions: max{FSP(age,3000), FSP(age,5000), FSP(age,9500), FSP(age,9900), FSP(age,9950), FSP(age,9990), FSP(age,9995), FSP(age,9999), FSP(age,99999)}. MathSelect: criterion for assessing the quality of the fitted total individual height function T(age) by combining nine parameters: Torigin, AgeP50, AgeP5, AgeP95, AgeP99, TPHV, TTONSET, TEND, TTONSET, TEND, TTONSET, TEND, TTONSET, TEND. TPHV: visually estimated age at peak height velocity; P(max) = 0.95*P(max); PHV: Peak height velocity; P(max) = 0.95*P(max); PHV: Peak height velocity; P(max) = 0.95*P(max). The authors are grateful for the contributions of the school nurses in the participating schools and the study team of I Larsson, A Olsson, B SamueIsen, and L Wirén for the collection of the original data. We would also like to thank the staff and all the students of the 11th grade 1992 of the Gothenburg schools. Deep thanks to A Ericson and B Svensson who
computerized all the original data and made the original visual inspection for PHV and adult height. Thanks for knowledgeable editing and language revision by Harriet Crofts.

Funding
The authors acknowledge financial support from the Swedish Research Council (VR no 7509), EpLife-TEENS research program (FORTE), Pfizer AB, the Governmental Grants for University Hospital Research (ALF), from RegionVästra Götaland, PhD-grants from the Southern Swedish healthcare region, the R&D department, County of Halland, and the Foundation Växthuset for children. The funding bodies were not involved in the design of the study, data collection, analysis or interpretation of data or in the writing of the manuscript.

Availability of data and materials
The present dataset for the analyses was made as described in the method section. This data used for the present dataset was after administrative permissions obtained from the ‘GrowUp Gothenburg study Database’, and is now a part of this database, which is stored in a server at the Gothenburg University. Swedish Data protection Act (1998:204) does not permit sensitive data on humans (like the GrowUp Questionnaires) to be openly shared. However, the authors are positive to collaborate with researchers worldwide. The data are available upon request from the principle Investigator Kerstin Albertsson-Wikland (Kerstin.albertsson.wikland@gu.se); depending on the research question, ethical approval might be required.

Authors’ contributions
KAW is the principal investigator of the study population used. AFMN performed the modeling work for the QEPS-model described here with contributions from AH, AN, LG, SA, and KAW on the specific pubertal growth estimates. AN performed the statistical analysis in SAS. AH performed the visual growth curve analysis of all individual growth charts, with second opinions from AN, SA, and KAW in unclear cases. AH, AN, LG, SA, AFMN, and KAW have all given substantial contribution to the conception, design, analysis and interpretation of these data, where all involved in writing the manuscript and also revised it critically for intellectual content, as well as giving approval for the final version of the manuscript to be submitted for publication.

Competing interests
AH has received an independent research grant from Pfizer AB. AFMN works for Muvara, Multivariate Analysis of Research Data, Statistical Consultation, The Netherlands. AN, LG, SA, and KAW declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Ethical approval was obtained from the ethics committee of the University of Gothenburg (91–92/131–93), and individual written consent was given by the participants of the 1974 cohort study if they were 18 years or older, or by their legal guardian if they were not old enough to give consent (16 to 18 years of age).

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Received: 18 February 2016 Accepted: 1 April 2017
Published online: 19 April 2017

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