Novel Type of References for Weight Aligned for Onset of Puberty – Using the Qeps Growth Model

Kerstin Albertsson-Wikland (✉ kerstin.albertsson.wikland@gu.se)

University of Gothenburg

Aimon Niklasson

University of Gothenburg

Lars Gelander

University of Gothenburg

Anton Holmgren

University of Gothenburg

Andreas Nierop

University of Gothenburg

Research Article

Keywords: pubertal growth, personalized growth, biological age, SDS, weight status, longitudinal BMI-selection, reference population

Posted Date: June 1st, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-429731/v2>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at BMC Pediatrics on November 13th, 2021. See the published version at <https://doi.org/10.1186/s12887-021-02954-z>.

Novel type of references for weight aligned for onset of puberty – using the QEPS growth model

Kerstin Albertsson-Wikland^{1*}, Aimon Niklasson², Lars Gelander¹, Anton Holmgren^{2,3},
Andreas F.M. Nierop^{1,4}

¹*Department of Physiology/Endocrinology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden*

²*Göteborg Pediatric Growth Research Center, Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sweden*

³*Department of Pediatrics, Halmstad Hospital, Halmstad, Sweden*

⁴*Muvara bv, Multivariate Analysis of Research Data, Leiderdorp, The Netherlands*

Correspondence: Kerstin Albertsson-Wikland, MD, PhD, Professor; Department of Physiology/Endocrinology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, SE 405 30 Gothenburg, Sweden; Kerstin.albertsson.wikland@gu.se Phone: +46 708 82 89 90

Short title: Pubertal weight reference

Orchid numbers: <https://orcid.org/>

KAW: 0000-0003-3167-0667; email Kerstin.albertsson.wikland@gu.se

AN: 0000-00001-5839-4207; email Aimon@bahnhof.se; aimon.niklasson@gu.se

LG: email Lars.gelander@vgregion.se; lars.gelander@gu.se

AH: 0000-0003-0940-8726; email Anton.holmgren@regionhalland.se; anton.holmgren@gu.se

AFMN: 0000-0002-6709-4836; nierop@muvara.nl; andreas.nierop@gu.se

Keywords: pubertal growth, personalized growth, biological age, SDS, weight status, longitudinal BMI-selection; reference population

Abstract

Background: Growth references are traditionally constructed relative to chronological age, despite inter-individual variations in pubertal timing. A new type of height reference was recently developed allowing growth to be aligned based on onset of pubertal growth. We here aim to develop a corresponding reference for pubertal weight.

Methods: To model QEPS-weight, 3595 subjects (1779 girls) from GrowUp₁₉₇₄Gothenburg and GrowUp₁₉₉₀Gothenburg were used. The QEPS-height-model was transformed to a corresponding QEPS-weight-model; thereafter, QEPS-weight was modified by an individual, constitutional weight-height-factor. Longitudinal weight and length/height measurements from 1418 individuals (698 girls) from GrowUp₁₉₉₀Gothenburg were then used to create weight references aligned for height at pubertal onset (the age at 5% of P-function growth, AgeP5). GrowUp₁₉₇₄Gothenburg subgroups based on pubertal timing, stature at pubertal onset, and childhood body composition were assessed using the references.

Results: References (median, SDS) for total weight (QEPS-functions), weight specific to puberty (P-function), and weight gain in the absence of specific pubertal growth (basic weight, QES-functions), allowing alignment of individual growth based on age at pubertal onset. For both sexes, basic weight was greater than average for late maturing, tall and high-BMI subgroups. The P-function-related weight was greater than average in short and lower than average in tall children, in those with high BMI, and in girls but not boys with low BMI.

Conclusions: New pubertal weight references allow individual variations in pubertal timing to be taken into consideration when evaluating growth. When used together with the comparable pubertal height reference, this will improve growth monitoring in clinical practice for identifying abnormal growth, and serve as a valuable research tool providing insight into human growth.

Background

The growth curve of an individual child reflects both the physical and psychosocial wellbeing of that child. According to the World Health Organization (WHO), every child has the right to grow and be healthy, and growth references or standards are crucial tools for monitoring such growth (1). It is therefore important that repeated height and weight measurements are obtained for every child within a healthcare setting, and plotted alongside established growth references, preferably using a computerized system (1-3). In order to be optimal, references should be constructed using data from children growing optimally. Height references should be updated regularly in countries where the population is still experiencing a secular trend for height to increase over time, as was recently done in Sweden (4). Similarly, in some countries, updates to weight references should consider that weight development may be unhealthy in children and adolescents owing to the ongoing obesity epidemic. This issue was addressed in the newly updated references for weight in Sweden by omitting individuals with extreme obesity from the longitudinal BMI data set used to develop the tool (5).

Growth references, both for height and weight, are traditionally presented in relation to chronological age. This remains the case despite the understanding that there is a broad variation in biological age between individuals, especially during puberty (3, 6). As a result of the reliance on chronological age, these references are of limited use for detecting abnormal growth during adolescence. Since the year 2000, Swedish healthcare systems have used references that incorporate an estimate of ongoing, basic, childhood growth based on the childhood growth function from the ICP-growth model (7-10). Use of this growth function has proved helpful in distinguishing ‘healthy’ late maturers from individuals with growth failure owing to an underlying condition or disease.’ When developing the most recent Swedish height references using a cohort of children born in 1990, this type of ‘prepubertal’

height reference showing ongoing basic growth was produced using the QE-functions of the QEPS-model (11, 12). The QEPS-model describes individual growth using four mathematical functions: a Q (Quadratic) and E (Exponential) arising before birth and resulting in the basic growth, to which a specific pubertal growth function, P, is added; growth is ended by an S (stop) function (11). We were recently able to develop and publish a completely new type of height reference describing growth resulting from the specific pubertal growth function of the QEPS model. This reference allows the height of the individual to be aligned relative to the onset of pubertal growth, and provides information on total growth, as well as separating growth that is a specific result of puberty from ongoing, basic growth that is continuing during the pubertal years (13, 14). As changes in height and weight should ideally be evaluated simultaneously, there remains a need for a corresponding reference for both prepubertal and pubertal weight.

The aim of this study was to use the QEPS-model to develop new references for weight during adolescence taking biological maturation into account. The weight references will be constructed using data from a homogeneous, longitudinally followed population of healthy children born at term to non-smoking mothers and Nordic parents, selected from the GrowUp₁₉₉₀Gothenburg cohort born in Sweden in around 1990 (5). It will be possible to use the weight references to evaluate pubertal growth in a child, irrespective of the chronological age at which pubertal growth begins in that individual. Separate references will be available for (i) total weight (modeled by the Q, E, P and S functions), (ii) weight gain that is specific to puberty (by the P function), and (iii) weight gain in the absence of growth specific to puberty (basic weight growth) (by the Q, E and S functions). We will also explore the usefulness of the new references for monitoring weight by analyzing subgroups of children

from the GrowUp₁₉₇₄Gothenburg cohort categorized according to the timing of puberty (early, average, late), height at start of puberty (tall, short) and body composition during childhood (high body mass index (BMI), low BMI), as used for exploring the comparable pubertal height reference (14).

Methods

Materials

1. Subset selection from GrowUp₁₉₇₄ & ₁₉₉₀Gothenburg cohorts for modelling QEPS weight

Data were retrieved from two community based observational growth studies conducted in high schools in Gothenburg, Sweden: GrowUp₁₉₇₄Gothenburg and GrowUp₁₉₉₀Gothenburg (9, 15, 16). Individuals with extreme BMI values relative to the GrowUp₁₉₇₄Gothenburg BMI_{SDS} reference (5), were excluded from both cohorts, leaving 2177 individuals (1081 girls) from GrowUp₁₉₇₄Gothenburg and 1418 individuals (698 girls) from GrowUp₁₉₉₀Gothenburg. The latter cohort served as the reference population for the recently published LMS weight, weight-for-height, and BMI references (5). Both cohorts were combined to form a group of 3595 subjects (1779 girls) which was used to construct the QEPS weight model needed for developing the references.

2. Reference population from GrowUp₁₉₉₀Gothenburg cohort

The QEPS weight reference population included 1418 individuals (698 girls) from the GrowUp₁₉₉₀Gothenburg cohort; this was the same cohort used to create the previously published LMS total weight, weight-for-height, and BMI references (see Supplemental Table

S1 of(5)). Children in this cohort were healthy (see Table 1 of(5)), born between 1989 and 1991 at full term (gestational age (GA) 37–43 weeks) in Sweden to Nordic parents with non-smoking mothers, and had information available on longitudinal growth until adult height. For more information see Albertsson-Wikland et al (5, 13).

3. Subgroups in the GrowUp₁₉₇₄Gothenburg cohort used for exploring the novel reference

Data from subgroups of healthy children from the GrowUp₁₉₇₄Gothenburg cohort (2177 subjects; 1081 girls) were used in order to explore the utility of the new pubertal weight reference as a research tool. These investigations looked in turn at the impact of grouping children according to age at onset of puberty, height at onset of puberty and childhood BMI. *According to pubertal age:* early (<-1.5 yrs), average (± 0.25 yrs) or late ($>+1.5$ yrs) onset of puberty (see Supplemental Table S3 of(14)); when age at TPHV (PHV from the total height growth curve) was used to estimate pubertal age. *According to height:* tall ($>+1.5$ SDS) or short (<-1.5 SDS) stature at onset of puberty. *According to childhood BMI:* high BMI ($>+1.5$ SDS) or low BMI (<-1.5 SDS).

QEPS weight method

The QEPS height model (11), was first transformed to a corresponding QEPS weight model. For detailed information see Supplemental for QEPS-weight model, including Supplemental Figure S1, S2, S3. QEPS weight was thereafter modified by an individual constitutional factor, a so-called weight-height-factor (*WHF*): $WHF=0$ stands for a ‘normal body constitution’, $WHF>0$ for a heavier than normal and $WHF<0$ for a leaner than normal body

constitution. Traditional references for total and prepubertal weight according to chronological age were computed in two steps comparable to the ‘QEPS method used for the references’ section in Supplement of (13), but with QEPS height functions replaced by corresponding QEPS weight functions fitted on observed individual weight data, referred to as the QEPS weight method.

We compared the total weight references obtained using the QEPS weight method with the previously published weight reference obtained by applying the LMS method (5). Both references were generated using data from the same population, Supplemental Figure S4. The two mean reference curves were similar; however, variance was smaller for the QEPS-derived compared with the LMS-derived reference became smaller, since it was based on fitted weight functions, excluding all sorts of weight error, whereas the LMS-derived reference was fitted on the observed weight measurements, including such error.

Thereafter, a new type of reference was generated for pubertal weight designed so that growth was aligned according to onset of puberty for the individual, identified based on height-specific *P*-function growth, defined as *AgeP5*, when 5% of height *Pmax* was obtained (Supplemental Figure S2 (14)) (12). All longitudinal QEPS weight functions for individuals in the reference population were aligned according to height *AgeP5*. For more information see Supplement.

Results

1. Total and prepubertal/basic weight references vs chronological age

Figure 1 shows the novel weight reference in kg (left axis) and in $\text{kg}^{0.5}$ (right axis) according to chronological age for girls and boys aged 4–20 years. Total weight is shown in color, with weight gained independently of puberty (the prepubertal, basic (QES-function) weight reference) shown in black.

Legend Figure 1: Chronological age reference for total and basic growth. References for weight (total weight and weight gained independently of puberty (basic growth = QES-function)) for girls (left) and boys (right) aged 4–20 years. Mean *total weight* (red/blue solid line, $\pm 1\text{SDS}$ (red/blue dotted line), and $\pm 2\text{SDS}$ (red/blue dashed line) and mean *basic weight* (black).

2. Weight references aligned for onset of puberty

Figure 2 shows the reference for total (QEPS) and basic (QES-function) weight in kg (left axis) and $\text{kg}^{0.5}$ (right axis) for girls and boys aligned according to the onset of puberty, estimated as AgeP5. In Figure 2 lower panel, specific P-function growth has been included alongside the curves shown in Figure 2 upper panel. To capture changes in weight relative to the acceleration in height that occurs during puberty, weight references in both figures are depicted from 4 years before to 10 years after the onset of the pubertal growth spurt.

Legend Figure 2 upper panel: References in kg (left axis) and in $\text{kg}^{0.5}$ (right axis) for total weight and the prepubertal/basic weight (weight gained independently of puberty (QES-function) for girls (red, left) and boys (blue, right). Curves are aligned for age at onset of pubertal growth spurt. Mean *total weight* (red/blue solid line, $\pm 1\text{SDS}$ (red/blue dotted line), and $\pm 2\text{SDS}$ (red/blue dashed line) and mean *basic weight* (black). **Figure 2 lower panel:** References shown in Figure 2 upper panel with the addition of a puberty-specific weight reference showing weight gain resulting from the P-function of the QEPS (P weight). *Specific P-function-derived weight* as mean, $\pm 1\text{SDS}$ (dotted line), and $\pm 2\text{SDS}$ (dashed line). The individual onset of puberty was identified and aligned based on the age at which 5% (AgeP5) of the total specific P-function growth (Pmax) had occurred.

3. *Rational for a puberty-aligned weight reference*

Figure 3 shows total weight relative to chronological age for subgroups of girls and boys with an early, average, and late onset of puberty. As expected, weight gain occurred sooner than average in children with an early onset of puberty, and later than average in children with a late onset of puberty. Thus, highlighting the inadequate usefulness for many adolescents of an ordinary chronological age weight reference due to the broad variation in chronological age at pubertal maturation within a population.

Legend Figure 3: Mean total weight (in kg, top; in SDS with 95% CI, bottom) according to chronological age for girls (left) and boys (right) from the GrowUp₁₉₇₄ Gothenburg cohort grouped according to onset of puberty (early, <-1.5 yrs (---), average, ± 0.25 yrs (•••), and late, $>+1.5$ yrs (—)). Data are visualized alongside the reference for total mean weight (thick solid lines) and ± 2 SDS (dotted red (left) and blue (right) lines).

4. Exploring pubertal weight in subgroups from the GrowUp₁₉₇₄Gothenburg cohort

Timing of puberty: Figure 4 shows weight (total (QEPS), basic (QES) and pubertal (P-function)) relative to the onset of puberty for subgroups of girls and boys with an early, average, and late onset of puberty. The basic component of weight gain was lower than average in the early puberty group and higher than average in the late puberty group. Specific weight gain during puberty was similar for all three groups. Total weight gain was similar in all groups

Legend Figure 4. Mean total, basic and puberty-specific weight gain (in kg, top; in SDS with 95% CI, bottom) relative to onset of puberty for girls (red at the top) and boys (blue at the bottom) grouped according to onset of puberty (early, <-1.5 yrs (---), average, ± 0.25 yrs (•••), and late, $>+1.5$ yrs (- — -)). Mean total weight (left panels), basic weight growth (middle panels), and specific pubertal weight growth (right panels) from the GrowUp₁₉₇₄Gothenburg cohort. Curves are aligned for age at onset of pubertal growth spurt. Data are visualized alongside the new reference for total mean weight (thick blue solid lines) and ± 2 SDS (dotted blue lines).

Stature: Figure 5 shows weight (total (QEPS), basic (QES) and pubertal (P-function)) for girls and boys according to height at the onset of puberty. The basic component of weight gain was higher than average in girls and boys classed as tall at the onset of puberty, and lower than average in girls and boys classed as short. In contrast, specific weight gain during puberty was lower than average for the tall group and higher than average for the short group.

Legend Figure 5: Mean total, basic and puberty-specific weight gain (in kg, top; in SDS with 95% CI, bottom) relative to the onset of puberty for girls (red at the top) and boys (blue at the bottom) according to height at the onset of puberty (tall, $>+1.5$ SDS (- — -) and short, <-1.5 SDS (- - -)). Mean total weight (left panels), basic weight growth (middle panels), and specific pubertal weight growth (right panels) from the GrowUp₁₉₇₄Gothenburg cohort. Curves are aligned for age at onset of pubertal growth spurt. Data are visualized alongside the new reference for total mean weight (thick red solid lines) and ± 2 SDS (dotted red lines).

Body Size: Figure 6 shows weight (total (QEPS), basic (QES) and pubertal (P-function)) for girls and boys according to BMI during childhood. The basic component of weight gain was higher than average in the high BMI group and lower than average in the low BMI group. Puberty-specific weight gain differed between the sexes: weight gain specific to the pubertal function was slightly lower than average in both the high and low BMI groups for girls, but in only the high BMI group for boys. Specific pubertal weight gain for boys in the low BMI group was similar to the average for the whole population.

Legend Figure 6: Total, basic and puberty-specific weight gain (in kg, top; in SDS with 95%CI, bottom) relative to the onset of puberty for girls (red at the top) and boys (blue at the bottom) according to BMI in childhood (high BMI, $>+1.5\text{SDS}$ (— —) and low BMI, $<-1.5\text{SDS}$ (- - -)). Mean total weight (left panels), basic growth (middle panels), and specific pubertal growth (right panels) in girls and boys from the GrowUp₁₉₇₄Gothenburg cohort. Curves are aligned for age at onset of pubertal growth spurt. Data are visualized alongside the new reference for total mean weight (thick red solid lines) and $\pm 2\text{SDS}$.

5. Using the new pubertal growth charts prospectively for an individual child

A manual procedure can be undertaken in order to monitor pubertal growth prospectively for an individual child using the new pubertal-age-growth charts developed from the pubertal-age-adjusted reference. A growth chart with both total and prepubertal height (13), as well as the present weight references, should be used for easy identification of the ‘height-take off’ at the start of puberty (13). Figure 7 describes how to use the pubertal-age-adjusted reference prospectively to assess total weight.

Legend Figure 7: A guide for prospective use of the pubertal-age-adjusted reference for total weight (kg and $\sqrt{\text{kg}}$) and height (cm) for girls (♀) and boys (♂). Individual age adjustment is made only from the height measurement at the chronological age (C-age) at which puberty started (see upper left traditional C-age-reference for girls and boys) (14), by using the height increase from the individual prepubertal growth curve (as drawn in upper left panel) through the individual measuring points. This occurs when secondary sex

characteristics develop; early breast development stage, B2 in girls (red, upper left panel), or testicular volume increase to 4-6 ml in boys (blue, upper left panel).. Height and weight according to C-age and P-age, ie the age adjusted to reflect the start of puberty are shown for an 8-year-old girl and a 13-year-old boy (14). Height (cm) and weight (in kg or $\sqrt{\text{kg}}$) according to C-age at the onset of puberty, and to P-age, after adjustment for age at onset of the pubertal growth spurt are depicted as red dots (all panels), based only on age in the height references for each sex respectively. Corresponding heights and weights are then moved to puberty-adjusted age = zero, in the P-age-references shown in the lower panels (left panels for height and right for weight). Thereafter, all measured heights and weights are depicted at ages/times recalculated in relation to the specific onset of puberty in that individual, labelled on the x-axis as ‘Time from onset of growth spurt (years)’. Thus, changes in weight and height in the years preceding the pubertal growth spurt can be evaluated using the novel reference. Note, the weight increase precedes the height increase in relation to puberty.

Discussion

New prepubertal and pubertal weight references

We present the first pubertal weight references to be developed that can be adjusted to reflect the biological maturation of the individual child. The new references include median values and SDS that allow alignment of individual weight data based on the time/age at onset of the pubertal growth spurt. These references were created using the growth functions of the QEPS-model which have previously been successfully applied to create a height reference that can be aligned for the onset of pubertal growth in the individual (14). By enabling the clinician to simultaneously adjust both weight and height based on the maturational stage of the individual, these two references promise to improve the precision of the evaluation of growth during adolescence (14).

As well as enabling weight to be assessed relative to maturational stage, the weight references generated allow us to look separately at the prepubertal and pubertal components of weight gain. By separating weight gain related specifically to puberty (P-function) from other weight gain (QE-function), it is possible to look at ongoing, basic weight gain during adolescence that is unrelated to puberty. Thus, these references will form a novel tool with which to investigate both puberty-independent and puberty-dependent changes in weight.

Weight changes precede height changes

By virtue of the alignment of weight data with the onset of the pubertal growth spurt, these references will allow us to look in more detail at the changes in weight that are known to precede the increase in height associated with the onset of puberty. Changes in weight before the acceleration of growth during puberty were already shown by Backman almost a century ago (17). It is well established that pubertal growth begins with characteristic sex-specific changes in body fat mass, that occur earlier in girls than boys, and this suggests a link between energy storage in adipose tissue and pubertal maturation (18). The new references will be new tool separating weight in relation to pubertal onset and by that increase our knowledge about changes in weight before the increase in height associated with puberty (Supplemental Figure S3).

Usefulness of a reference separating the growth functions during puberty

The benefit of using a growth model is not only to describe growth but also to be able to analyse how different growth functions can be related to the mechanisms underlying the regulation of growth (19, 20). Here, thanks to the mathematical growth functions from the

QEPS-weight and the QEPS-height models, we present a tool for investigating weight gain in new ways and with higher precision than previously possible. In this analysis, we explored differences in weight gain between groups of children with different characteristics prior to entering puberty. A novel finding from this analysis was that basic weight gain was greater in boys and girls who were late maturers or tall at the start of puberty, when compared to either the reference, or those of average pubertal timing or stature. The contrary, with lower than average basic weight gain, was found for those who underwent early pubertal maturation or had short stature. P-function related weight gain was greater than average in short individuals and lower than average in tall individuals. Previously, we investigated children with different BMI, and found a positive relationship between BMI and greater than average gains in basic height and lower than average gains in puberty-specific height (21). Results from the present study extend these findings, showing that a high BMI is also associated with greater than average gains in basic weight and lower than average gains in puberty-specific weight, and that low BMI is associated with lower than average increases in basic weight. In addition, a sex-specific difference was found for specific pubertal growth, which was lower than average in girls, and average in boys.

A QEPS-weight model behind puberty-aligned weight references

Developing references for weight that are aligned for individual onset of puberty, require a growth model for individual weight. As only a model for weight in infancy and early childhood was available (22-25), we had to develop a model for the entire growth period that was good enough for this purpose. We also had to deal with the problem that weight measurements are known to be subject to greater daily variations than are expected for measurements of height. We therefore took the approach of transforming height values into

corresponding values for weight in order to develop the weight model. Thus, the QEPS-weight model was supported by a transformation of fitted QEPS-height functions (11), into corresponding QEPS-weight functions. For better fitting results, introduction of only one individual factor was necessary; a specific individual weight parameter (*WHF*) in the weight model that was not predicted by height. However, the QEPS-weight model could also have been constructed and fitted directly on observed weight measurements using the six individual weight parameters, while optimizing the basic four shape-invariant QEPS-weight functions. In our experience, it would have resulted in considerable overfitting of the weight measurements, because of higher standard error of the fit for weight than for height. For height, the residual error was mostly owing to measurement error and time of day, whereas for weight, the residual variation was caused by many factors and could not simply be explained. Residual variation around individual predicted weight for normal body constitution might, for instance, also be related to individual variation in the relationship of fat /muscle distributions as estimated by body compartment analyses (DEXA) or subcutaneous fat measures, waist circumference or other comparable measurements. There are models for human growth and body dynamics (26). Here, we have tried to find a good enough QEPS-weight model using the individual height information, however, other approaches or fine-tuning of the method remains to be developed.

Biological correlates of individual WHF

The introduction of an individual WHF originated from the improved fitting of the model, described above and in Supplement. This gives rise to the question as to whether there is any biological correlate /connection to this factor. Adult height of an individual can fairly accurate be predicted by growth during infancy (ie attained height at 2 years of age), and

382 delayed timing of transition from infancy to childhood growth corresponds to reduced adult
383 height. Thus, it seems that there is a critical window in early life for changes in growth (19).
384 Moreover, clinically, there also appears to be a critical window during infancy for changing
385 body size (correlate to WHF); it is known to be extremely difficult to change body size later
386 on in life, if a child was thin (low WHF) or obese (high WHF) during infancy (27). There is
387 increasing evidence of a role for epigenetic programming during prenatal and early postnatal
388 periods in determining child growth and development and later development of diseases. For
389 instance, prenatal epigenetics have been shown to change IGF-I expression in several ways
390 (28-30), and the Dutch Famine showed that famine during early and mid-gestation affects
391 metabolism later in life, including increased risk for obesity(31). There is also increasing
392 evidence that variations in early postnatal nutrition have epigenetic effects on developmental
393 programming and may result in the development of cardiovascular diseases, overweight,
394 obesity, diabetes, and other chronic conditions (32-35).

396 **Prospective monitoring of growth in individual children using the new references and** 397 **future perspectives**

398 These new weight references will allow the creation of updated computerized references for
399 use in healthcare settings. Until computerized versions of the puberty-aligned references for
400 height and weight are available, a manual procedure can be undertaken in order to monitor
401 pubertal growth prospectively for an individual child using the new references (see Figure 7).
402 A growth chart with both total and prepubertal height (13), as well as the present weight
403 references, should be used for easy identification of the ‘height-take off’ at the start of
404 puberty(13). The use of these new references will help to determine whether or not we should
405 be concerned about the growth of late-maturing children who appear to be underweight, or

early-maturing children who appear to be overweight, based on assessments relative to chronological age. The availability of this type of reference is an important step towards more meaningful and informative monitoring of weight development of an individual during the adolescent years. The next step will be to develop references for other growth-related parameters, such as BMI.

Conclusion

We here present new types of weight references both for prepubertal weight in relation to chronological age, and for weight during pubertal years aligned for the onset of the pubertal growth spurt in the individual. When used together with the prepubertal and pubertal height references (13, 14), the new weight references will allow for improved growth monitoring during adolescence for detecting abnormal growth. The new references will also serve as valuable research tools that will help to provide new insights into human growth.

Declarations:

Ethical approval: Ethical approval was obtained from the Regional Ethics Review Board in Gothenburg, (Ad 91-92/131 -93 and Ad 444-08 T062-09). Informed consent was given by participants and parents of individuals <18 years of age. Studies were conducted in accordance with the principles of the Declaration of Helsinki.

Consent of Publications: Not Applicable

Availability of data and materials: the generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request

Competing interest: AFMN works for Muvara, Multivariate Analysis of Research Data, Statistical Consultation, the Netherlands. KAW, AN, AH, and LG declare that they have no competing interests.

Research funding: The authors acknowledge financial support from the Governmental grants under the ALF agreement, ALFGBG-719041, ALFGBG-812951, the Region Halland Grants, and the Foundation Vårhuset for children.

Author contributions: KAW is the principal investigator of the study populations used. AFMN performed the modeling work for the QEPS model described here and made the QEPS function estimations, reference values, and Figures 1-6 & Supplemental Figures S1-S4. AN made Figure 7 and statistics. KAW, AN, AH, LG, and AFMN have all made a substantial contribution to the conception, design, analysis, and interpretation of these data. KAW wrote the first draft and AFMN the methods part. All authors revised the manuscript critically for intellectual content and approved the final version to be submitted for publication.

Acknowledgements: The authors are grateful for the contributions of the students of the 12th grade 1998/9 from the Gothenburg area schools, and their school nurses; the study team led by C Pfeiffer-Mosesson and A Olsson; for Data support given by L Ljungberg and B Bengtsson and for careful editing and language revision by H Crofts.

452 REFERENCES

- 453 1. Who Multicentre Growth Reference Study G, de Onis M. WHO Child Growth
454 Standards based on length/height, weight and age. *Acta Paediatrica*. 2006; 95:76-85
- 455 2. Sankilampi U, Saari A, Laine T, Miettinen PJ, Dunkel L. Use of electronic health records
456 for automated screening of growth disorders in primary care. *JAMA*. 2013; 310:1071-2
- 457 3. Cole TJ. The development of growth references and growth charts. *Annals of human*
458 *biology*. 2012; 39:382-94
- 459 4. Holmgren A, Niklasson A, Aronson AS, Sjöberg A, Lissner L, Albertsson-Wikland K.
460 Nordic populations are still getting taller - secular changes in height from the 20th to 21st century.
461 *Acta Paediatr*. 2019; 108:1311-20
- 462 5. Albertsson-Wikland K, Niklasson A, Gelander L, Holmgren A, Sjöberg A, Aronson AS, et
463 al. Swedish references for weight, weight-for-height and body mass index: The GrowUp 1990
464 Gothenburg study. *Acta Paediatr*. 2021; 110:537-48
- 465 6. Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height,
466 weight, height velocity, and weight velocity: British children, 1965. I. *Archives of disease in*
467 *childhood*. 1966; 41:454-71
- 468 7. Karlberg J. On the modelling of human growth. *Statistics in medicine*. 1987; 6:185-92
- 469 8. Karlberg J, Fryer JG, Engstrom I, Karlberg P. Analysis of linear growth using a
470 mathematical model. II. From 3 to 21 years of age. *Acta paediatrica Scandinavica*. 1987; 337:12-29
- 471 9. Albertsson-Wikland K, Luo ZC, Niklasson A, Karlberg J. Swedish population-based
472 longitudinal reference values from birth to 18 years of age for height, weight and head
473 circumference. *Acta Paediatr*. 2002; 91:739-54
- 474 10. Gelander L, Hagenäs L, Albertsson-Wikland K. Tillväxtkurvan i skolhälsovården. Tillväxt
475 och kroppslig mognad 6-18 år. Manual och Lilla tillväxtskolan. Stockholm: Kommentus; 2003
- 476 11. Nierop AF, Niklasson A, Holmgren A, Gelander L, Rosberg S, Albertsson-Wikland K.
477 Modelling individual longitudinal human growth from fetal to adult life - QEPS I. *J Theor Biol*. 2016;
478 406:143-65
- 479 12. Holmgren A, Niklasson A, Gelander L, Aronson AS, Nierop AFM, Albertsson-Wikland K.
480 Insight into human pubertal growth by applying the QEPS growth model. *BMC pediatrics*. 2017;
481 17:107
- 482 13. Albertsson-Wikland K, Niklasson A, Holmgren A, Gelander L, Nierop AFM. A new
483 Swedish reference for total and prepubertal height. *Acta Paediatr*. 2020; 109:754-63
- 484 14. Albertsson-Wikland KG, Niklasson A, Holmgren A, Gelander L, Nierop AFM. A new
485 type of pubertal height reference based on growth aligned for onset of pubertal growth. *J Pediatr*
486 *Endocrinol Metab*. 2020; 33:1173-82
- 487 15. Sjöberg A, Barrenäs ML, Brann E, Chaplin JE, Dahlgren J, Mårild S, et al. Body size and
488 lifestyle in an urban population entering adulthood: the 'Grow up Gothenburg' Study. *Acta Paediatr*.
489 2012; 101:964-72
- 490 16. Holmgren A, Niklasson A, Nierop AFM, Gelander L, Aronson AS, Sjöberg A, et al.
491 Estimating secular changes in longitudinal growth patterns underlying adult height with the QEPS
492 model: the Grow Up Gothenburg cohorts. *Pediatric research*. 2018; 84:41-9
- 493 17. Backman G. Gewichtswachstum des Mannes. *Wilhelm Roux' Archiv für*
494 *Entwicklungsmechanik der Organismen* 1940; 140:285–314
- 495 18. Vizmanos B, Marti-Henneberg C. Puberty begins with a characteristic subcutaneous
496 body fat mass in each sex. *European journal of clinical nutrition*. 2000; 54:203-8
- 497 19. Hochberg Z, Albertsson-Wikland K. Evo-Devo of Infantile and Childhood Growth.
498 *Pediatric research*. 2008; 64:2-7

20. Hochberg Z. *Evo-Devo of Child Growth: Treatise on Child Growth and Human Evolution*, First Edition.: Wiley-Blackwell, Publishers; 2012
21. Holmgren A, Niklasson A, Nierop AF, Gellander L, Aronson AS, Sjöberg A, et al. Pubertal height gain is inversely related to peak BMI in childhood. *Pediatric research*. 2017; 81:448–54
22. Beath KJ. Infant growth modelling using a shape invariant model with random effects. *Statistics in medicine*. 2007; 26:2547-64
23. Beath KJ. Infant growth modelling and assessment of Growth. In: Preedy VR, editor *Handbook of growth and Growth monitoring in health and disease*: Springer; 2012
24. Ahmadi S, Bodeau-Livinec F, Zoumenou R, Garcia A, Courtin D, Alao J, et al. Comparison of growth models to describe growth from birth to 6 years in a Beninese cohort of children with repeated measurements. *BMJ open*. 2020; 10:e035785
25. Botton J, Scherdel P, Regnault N, Heude B, Charles MA, Group EM-CCS. Postnatal weight and height growth modeling and prediction of body mass index as a function of time for the study of growth determinants. *Ann Nutr Metab*. 2014; 65:156-66
26. Rahmandad H. Human growth and body weight dynamics: an integrative systems model. *PLoS One*. 2014; 9:e114609
27. Koletzko B, Brands B, Poston L, Godfrey K, Demmelmair H, Early Nutrition P. Early nutrition programming of long-term health. *The Proceedings of the Nutrition Society*. 2012; 71:371-8
28. Fu Q, McKnight RA, Yu X, Wang L, Callaway CW, Lane RH. Uteroplacental insufficiency induces site-specific changes in histone H3 covalent modifications and affects DNA-histone H3 positioning in day 0 IUGR rat liver. *Physiological genomics*. 2004; 20:108-16
29. Tosh DN, Fu Q, Callaway CW, McKnight RA, McMillen IC, Ross MG, et al. Epigenetics of programmed obesity: alteration in IUGR rat hepatic IGF1 mRNA expression and histone structure in rapid vs. delayed postnatal catch-up growth. *Am J Physiol Gastrointest Liver Physiol*. 2010; 299:G1023-9
30. Zinkhan EK, Fu Q, Wang Y, Yu X, Callaway CW, Segar JL, et al. Maternal Hyperglycemia Disrupts Histone 3 Lysine 36 Trimethylation of the IGF-1 Gene. *Journal of nutrition and metabolism*. 2012; 2012:930364
31. Roseboom T, de Rooij S, Painter R. The Dutch famine and its long-term consequences for adult health. *Early human development*. 2006; 82:485-91
32. Barker DJ, Osmond C, Kajantie E, Eriksson JG. Growth and chronic disease: findings in the Helsinki Birth Cohort. *Annals of human biology*. 2009; 36:445-58
33. Eriksson JG, Forsen TJ, Kajantie E, Osmond C, Barker DJ. Childhood growth and hypertension in later life. *Hypertension*. 2007; 49:1415-21
34. Forsdahl A. Living conditions in childhood and subsequent development of risk factors for arteriosclerotic heart disease. The cardiovascular survey in Finnmark 1974-75. *Journal of epidemiology and community health*. 1978; 32:34-7
35. Barker DJ, Osmond C, Forsen TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. *The New England journal of medicine*. 2005; 353:1802-9

Legends to the Figures:

Legend Figure 1: Chronological age reference for total and basic growth. References for weight (total weight and weight gained independently of puberty (basic growth = QES-function)) for girls (left) and boys (right) aged 4–20 years. Mean *total weight* (red/blue solid line, ± 1 SDS (red/blue dotted line), and ± 2 SDS (red/blue dashed line) and mean *basic weight* (black).

Legend Figure 2 upper panel: References in kg (left axis) and in $\text{kg}^{0.5}$ (right axis) for total weight and the prepubertal/basic weight (weight gained independently of puberty (QES-function) for girls (red, left) and boys (blue, right)). Curves are aligned for age at onset of pubertal growth spurt. Mean *total weight* (red/blue solid line, ± 1 SDS (red/blue dotted line), and ± 2 SDS (red/blue dashed line) and mean *basic weight* (black). **Figure 2 lower panel:** References shown in Figure 2 upper panel with the addition of a puberty-specific weight reference showing weight gain resulting from the P-function of the QEPS (P weight). *Specific P-function-derived weight* as mean, ± 1 SDS (dotted line), and ± 2 SDS (dashed line). The individual onset of puberty was identified and aligned based on the age at which 5% (AgeP5) of the total specific P-function growth (Pmax) had occurred.

Legend Figure 3: Mean total weight (in kg, top; in SDS with 95% CI, bottom) according to chronological age for girls (left) and boys (right) from the GrowUp₁₉₇₄ Gothenburg cohort grouped according to onset of puberty (early, <-1.5 yrs (- - -), average, ± 0.25 yrs ($\bullet \bullet \bullet$), and late, $>+1.5$ yrs (- — -)). Data are visualized alongside the reference for total mean weight (thick solid lines) and ± 2 SDS (dotted red (left) and blue (right) lines).

Legend Figure 4. Mean total, basic and puberty-specific weight gain (in kg, top; in SDS with 95% CI, bottom) relative to onset of puberty for girls (red at the top) and boys (blue at the bottom) grouped according to onset of puberty (early, <-1.5 yrs (- - -), average, ± 0.25 yrs ($\bullet \bullet$), and late, $>+1.5$ yrs (- — -)). Mean total weight (left panels), basic weight growth (middle panels), and specific pubertal weight growth (right panels) from the GrowUp₁₉₇₄Gothenburg cohort. Curves are aligned for age at onset of pubertal growth spurt. Data are visualized alongside the new reference for total mean weight (thick blue solid lines) and ± 2 SDS (dotted blue lines).

Legend Figure 5: Mean total, basic and puberty-specific weight gain (in kg, top; in SDS with 95% CI, bottom) relative to the onset of puberty for girls (red at the top) and boys (blue at the bottom) according to height at the onset of puberty (tall, $>+1.5$ SDS (- — -) and short, <-1.5 SDS (- - -)). Mean total weight (left panels), basic weight growth (middle panels), and specific pubertal weight growth (right panels) from the GrowUp₁₉₇₄Gothenburg cohort. Curves are aligned for age at onset of pubertal growth spurt. Data are visualized alongside the new reference for total mean weight (thick red solid lines) and ± 2 SDS (dotted red lines).

Legend Figure 6: Total, basic and puberty-specific weight gain (in kg, top; in SDS with 95%CI, bottom) relative to the onset of puberty for girls (red at the top) and boys (blue at the bottom) according to BMI in childhood (high BMI, $>+1.5$ SDS (- — -) and low BMI, <-1.5 SDS (- - -)). Mean total weight (left panels), basic growth (middle panels), and specific pubertal growth (right panels) in girls and boys from the GrowUp₁₉₇₄Gothenburg cohort. Curves are aligned for age at onset of pubertal growth spurt. Data are visualized alongside the new reference for total mean weight (thick red solid lines) and ± 2 SDS.

592

593 **Legend Figure 7:** A guide for prospective use of the pubertal-age-adjusted reference for total
594 weight (kg and $\sqrt{\text{kg}}$) and height (cm) for girls (♀) and boys (♂).

595 Individual age adjustment is made only from the height measurement at the chronological age
596 (C-age) at which puberty started (see upper left traditional C-age-reference for girls and boys)
597 (14), by using the height increase from the individual prepubertal growth curve (as drawn in
598 upper left panel) through the individual measuring points. This occurs when secondary sex
599 characteristics develop; early breast development stage, B2 in girls (red, upper left panel), or
600 testicular volume increase to 4-6 ml in boys (blue, upper left panel)..

601 Height and weight according to C-age and P-age, ie the age adjusted to reflect the start of
602 puberty are shown for an 8-year-old girl and a 13-year-old boy (14). Height (cm) and weight
603 (in kg or $\sqrt{\text{kg}}$) according to C-age at the onset of puberty, and to P-age, after adjustment for
604 age at onset of the pubertal growth spurt are depicted as red dots (all panels), based only on
605 age in the height references for each sex respectively. Corresponding heights and weights are
606 then moved to puberty-adjusted age = zero, in the P-age-references shown in the lower panels
607 (left panels for height and right for weight). Thereafter, all measured heights and weights are
608 depicted at ages/times recalculated in relation to the specific onset of puberty in that
609 individual, labelled on the x-axis as 'Time from onset of growth spurt (years)'. Thus, changes
610 in weight and height in the years preceding the pubertal growth spurt can be evaluated using
611 the novel reference. Note, the weight increase *precedes* the height increase in relation to
612 puberty.

613

614

Figures

Figure 1

Chronological age reference for total and basic growth. References for weight (total weight and weight gained independently of puberty (basic growth = QES-function)) for girls (left) and boys (right) aged 4–20 years. Mean total weight (red/blue solid line, ± 1 SDS (red/blue dotted line), and ± 2 SDS (red/blue dashed line) and mean basic weight (black).

Figure 2

upper panel: References in kg (left axis) and in kg^{0.5} (right axis) for total weight and the prepubertal/basic weight (weight gained independently of puberty (QES- function) for girls (red, left) and boys (blue, right). Curves are aligned for age at onset of pubertal growth spurt. Mean total weight (red/blue solid line, ± 1 SDS (red/blue dotted line), and ± 2 SDS (red/blue dashed line) and mean basic weight (black). Figure 2 lower panel: References shown in Figure 2 upper panel with the addition of a

puberty-specific weight reference showing weight gain resulting from the P-function of the QEPS (P weight). Specific P-function-derived weight as mean, ± 1 SDS (dotted line), and ± 2 SDS (dashed line). The individual onset of puberty was identified and aligned based on the age at which 5% (AgeP5) 560 of the total specific P-function growth (Pmax) had occurred.

Figure 3

Mean total weight (in kg, top; in SDS with 95% CI, bottom) according to chronological age for girls (left) and boys (right) from the GrowUp1974 Gothenburg cohort grouped according to onset of puberty (early, <-1.5 yrs (---), average, ± 0.25 yrs (···), and late, $>+1.5$ yrs (—)). Data are visualized alongside the reference for total mean weight (thick solid lines) and ± 2 SDS (dotted red (left) and blue (right) lines).

Figure 4

Mean total, basic and puberty-specific weight gain (in kg, top; in SDS with 95% CI, bottom) relative to onset of puberty for girls (red at the top) and boys (blue at the bottom) grouped according to onset of puberty (early, <-1.5yrs (---), average, ±0.25yrs (•••), and late, >+1.5yrs (- — -)). Mean total weight (left panels), basic weight growth (middle panels), and specific pubertal weight growth (right panels) from the GrowUp1974Gothenburg cohort. Curves are aligned for age at onset of pubertal growth spurt. Data are

visualized alongside the new reference for total mean weight (thick blue solid lines) and ± 2 SDS (dotted blue lines).

Figure 5

Mean total, basic and puberty-specific weight gain (in kg, top; in SDS with 95% CI, bottom) relative to the onset of puberty for girls (red at the top) and boys (blue at the bottom) according to height at the onset of puberty (tall, $>+1.5$ SDS (- — -) and short, <-1.5 SDS (- - -)). Mean total weight (left panels), basic weight growth (middle panels), and specific pubertal weight growth (right panels) from the GrowUp1974Gothenburg cohort. Curves are aligned for age at onset of pubertal growth spurt. Data are visualized alongside the new reference for total mean weight (thick red solid lines) and ± 2 SDS (dotted red lines).

Figure 6

Total, basic and puberty-specific weight gain (in kg, top; in SDS with 95%CI, bottom) relative to the onset of puberty for girls (red at the top) and boys (blue at the bottom) according to BMI in childhood (high BMI, $>+1.5\text{SDS}$ (—) and low BMI, $<-1.5\text{SDS}$ (---)). Mean total weight (left panels), basic growth (middle panels), and specific pubertal growth (right panels) in girls and boys from the GrowUp1974Gothenburg

cohort. Curves are aligned for age at onset of pubertal growth spurt. Data are visualized alongside the new reference for total mean weight (thick red solid lines) and ± 2 SDS.

Figure 7

A guide for prospective use of the pubertal-age-adjusted reference for total weight (kg and $\sqrt{\text{kg}}$) and height (cm) for girls (♀) and boys (♂). Individual age adjustment is made only from the height measurement at the chronological age (C-age) at which puberty started (see upper left traditional C-age-reference for girls and boys) (14), by using the height increase from the individual prepubertal growth curve (as drawn in upper left panel) through the individual measuring points. This occurs when secondary sex characteristics develop; early breast development stage, B2 in girls (red, upper left panel), or testicular volume increase to 4-6 ml in boys (blue, upper left panel).. Height and weight according to C-age and P-age, ie the age adjusted to reflect the start of puberty are shown for an 8-year-old girl and a 13-year-old boy (14). Height (cm) and weight (in kg or $\sqrt{\text{kg}}$) according to C-age at the onset of puberty, and to P-age, after adjustment for age at onset of the pubertal growth spurt are depicted as red dots (all panels), based only on age in the height references for each sex respectively. Corresponding heights and weights are then moved to puberty-adjusted age = zero, in the P-age-references shown in the lower panels (left panels for height and right for weight). Thereafter, all measured heights and weights are depicted at ages/times recalculated in relation to the specific onset of puberty in that individual, labelled on the x-axis as 'Time from onset of growth spurt (years)'. Thus, changes in weight and height in the years preceding the pubertal growth spurt can be evaluated using the novel reference. Note, the weight increase precedes the height increase in relation to puberty.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Ref420210331suppl.pdf](#)