BRIEF COMMUNICATION | Genetics in Medicine

Longitudinal growth curves for children with classical osteogenesis imperfecta (types III and IV) caused by structural pathogenic variants in type I collagen

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Purpose: Growth deficiency is a cardinal feature of osteogenesis imperfecta (OI) types III and IV, caused by pathogenic variants in type I collagen. OI-specific longitudinal growth charts are needed for patient care.

Methods: We compiled longitudinal length, weight, head circumference, and body mass index (BMI) data from 100 children with types III and IV OI and known type I collagen pathogenic variants. Effects of gender, OI type, and pathogenic variant were examined using multilevel modeling. OI-specific centile curves were constructed using generalized additive model for location, scale, and shape (GAMLSS).

Results: OI type and gender, but not the specific mutated collagen gene, significantly affect stature, but only OI type affects weight. Head circumference was not significantly different by gender, type, or mutated gene. In both genders, length curves for types III and IV OI overlap and the type IV 95th centile curve overlaps the lower US Centers for Disease Control and Prevention (CDC) curves for the general population. A pubertal growth spurt is generally absent or blunted in types III/IV OI. The body mass index 50th and 95th centile curves are distinctly shifted above respective US CDC curves in both genders.

Conclusions: OI type is a stronger contributing factor than gender for OI growth, while curves do not differ for *COL1A1* versus *COL1A2* pathogenic variants. Types III and IV OI-specific growth curves are presented.

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Keywords: growth curves; osteogenesis imperfecta; type III OI; type IV OI

INTRODUCTION

Osteogenesis imperfecta (OI) is a well-known heritable disorder of connective tissue characterized by bone fragility and deformity.[1] Most patients with OI have autosomal dominantly inherited pathogenic variants in the type I collagen genes,[2] *COL1A1* or *COL1A2*[2], resulting in structurally abnormal collagen (OI types II, III, IV; OMIM 166210, 259420, and 166220, respectively) or a reduced amount of structurally normal collagen (OI type I, OMIM 166200). Nonlethal pathogenic variants causing types III and IV OI occur in both collagen chains, with a variety of substituting residues.[2]

Significant short stature is a cardinal feature of types III and IV OI, the progressively deforming and moderately severe forms, respectively. Growth deficiency is generally marked by the end of the first year of life and continues to progress thereafter.[3] Clinicians and families lack information necessary to monitor the growth of a child with OI. Difficulty in setting OI-specific growth expectations undermines detection of other medical conditions that involve growth failure.

Syndrome-specific growth charts are available for Down syndrome,[4] Turner syndrome,[5,6] and achondroplasia,[7] but not for the most common forms of OI. The aims of this study were (1) to delineate growth differences between classical OI patients based on gender, OI type (III versus IV), and location of pathogenic variant (*COL1A1* versus *COL1A2*); and (2) to construct standard length and weight growth curves, and derivative body mass index (BMI) curves for OI types III and IV.

MATERIALS AND METHODS

Growth parameters, length (cm), weight (kg), and head circumference (cm), were measured at the National Institutes of Health (NIH) Clinical Center in 100 patients with OI types

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III and IV caused by pathogenic variants in type I collagen. Patients were enrolled in the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) longitudinal pediatric OI study from 1986 to 2006. Parameters were measured at intervals that depended on the frequency of patient visits, with median interval of 5.4 months (median minimal and maximal intervals were 2.8 months and 16 months, respectively). All measurements were obtained and documented by research nurses who are well-versed in these measurements, and by using the same equipment for all patients. Informed consent was obtained from parents for each participant in an NICHD institutional review board (IRB)-approved protocol on OI natural history.

Demographics

Similar to Centers for Disease Control and Prevention (CDC) pediatric growth charts, our OI growth charts cover the age range of 2–16 years. The distribution of gender, OI type, and collagen pathogenic variants are shown in Table S1, as are the total numbers of measurements. The study includes data from 1480 length, 1502 weight, and 1398 head circumference observations. For comparison curves between major parameters (gender, OI type, pathogenic variant location), 55 patients are female, while 45 are male. Forty-five patients have type III (27 females), while 55 patients have type IV OI (28 females). Pathogenic variants in *COL1A1* are causative in 57 patients (30 type III OI), while *COL1A2* pathogenic variants are causative in 43 patients (15 type III OI). Patients with null *COL1A1* alleles were not included. Patients with scoliosis were included, because this is part of the natural history of OI contributing to short stature.

Statistics

Differences in growth curves based on gender, OI type, and location of pathogenic variant (*COL1A1* versus *COL1A2*) were analyzed using nonlinear multilevel modeling. Analyses estimated the sample average growth curves across age (years) and tested for population group differences in size (intercept), growth rate (slope), and curvature (acceleration) of the growth curves. Details are included in Supplementary Materials and Methods.

Standard growth curve construction

Centile curves were constructed using the generalized additive model for location, scale, and shape (GAMLSS)[8] package from the R statistical computing environment.[9] GAMLSS was adopted by the World Health Organization (WHO) in the development of its 2007 growth reference charts, and incorporates the LMS method[10] of curve smoothing used by the CDC to develop its 2000 growth charts.

Data were binned into half-year intervals, with the lowest bin at 1.5 years and the highest bin at 17.5 years, to generate curves for ages 2–16 years. Age bins covered a range of ± 0.25 years. Each patient was limited to one measurement per age bin per growth parameter. When patients had multiple assessments within the same half-year interval, the occasion that fell closest to the defined age bin or that provided the most complete information (i.e., had scores for the most growth parameters) was retained for analysis. Centile curves were constructed using the LMS method[10] and the extension of LMS developed by Rigby and Stasinopoulos. Details are provided in the Supplementary Materials and Methods.

RESULTS

OI type and gender, but not the specific mutated collagen chain, significantly influence length

For the comparison of length, weight, and head circumference between OI type, gender, and specific mutated collagen chain, we used a compilation of 100 individual longitudinal curves to generate projected trajectories of growth parameters (Fig. **1**). Length differed most significantly by OI type and was also significantly different by gender (Fig. **1a**). Males with OI are taller than females with OI at all ages (i.e., growth rate at 2 years old, 5.7 cm/year vs. 4.5 cm/year, $p < 0.05$; at 8 years old, 4.7 cm/year vs. 3.7 cm/year, $p < 0.05$; cf. Table S3a model 3), and the difference becomes larger with increasing age. Individuals with type IV OI are taller than those with type III OI at all ages (at 2, 8, and 16 years, in cm/year, 6.3 vs. 3.5, $p < 0.001$; 5.3 vs. 2.7, $p < 0.001$; 4.0 vs. 1.5, $p < 0.001$, respectively; cf. Table S3a model 2), and the difference increases with age. The composite curves for type IV are steeper than those for type III across the age span. However, we found no difference in length trajectory between OI caused by nonlethal pathogenic variants in *COL1A2* versus *COL1A1* (Fig. **1a**).

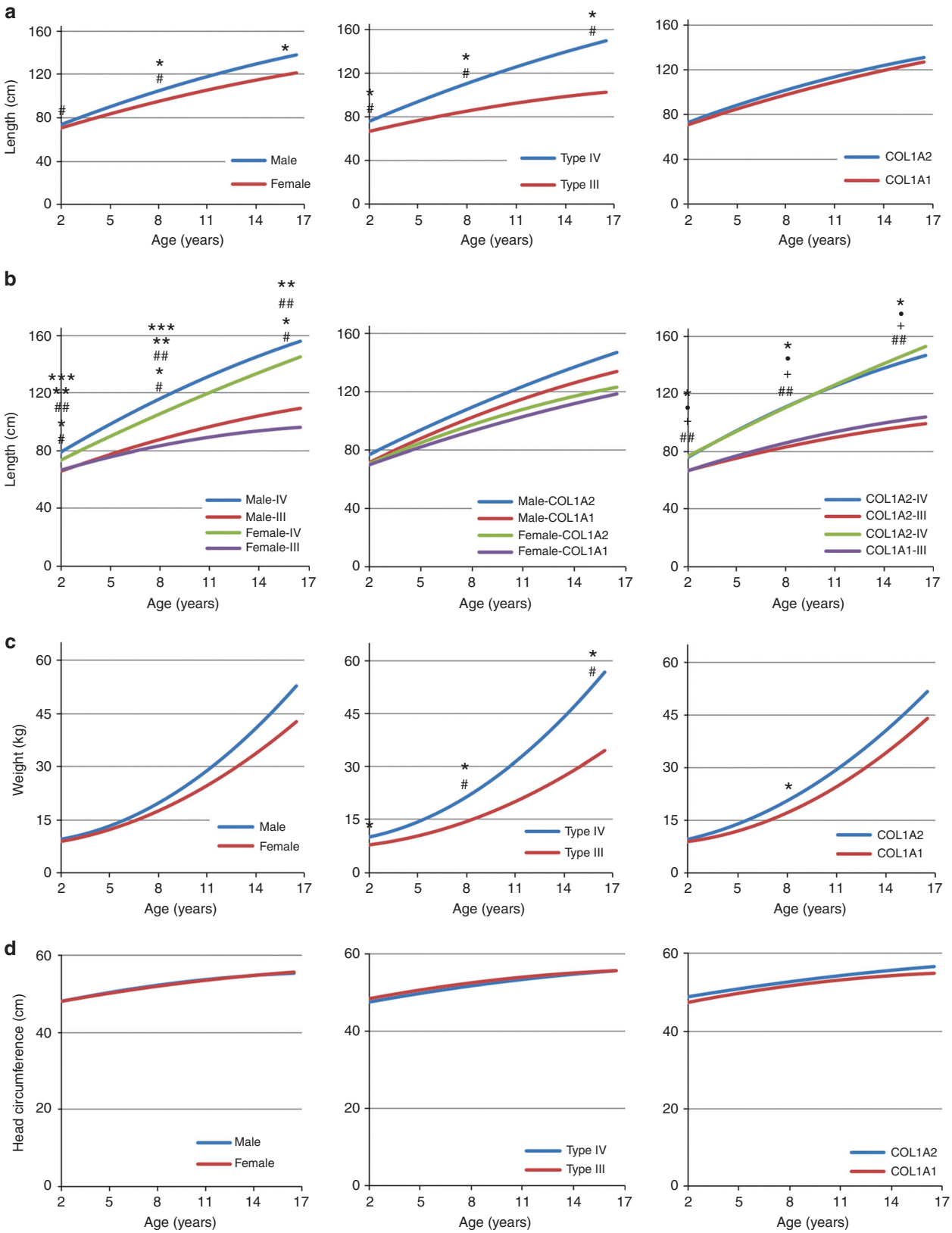
We further analyzed length trajectories using within-group comparisons among each gender, OI type, or mutant collagen chain (Fig. **1b**). Both males and females with type IV OI were taller than individuals with type III OI. Type IV boys have both taller and steeper curves than type IV girls. Type III boys and girls have similar growth as young children, but the slightly steeper type III male curve led to a significant difference in the late teen years. When length trajectories were analyzed by both mutant collagen chain and either gender or OI type, we again found no influence of the specific mutated collagen alpha chain.

Weight differs significantly by OI type, but not gender or mutated collagen chain

Weight trajectories do not differ significantly by gender but do differ by OI type. Type IV OI children, who are also taller than type III children, having significantly greater weight than those with type III throughout life (ages 2, 8, and 16 years: 10.1 vs. 8 kg, $p < 0.001$; 21.5 vs. 14.6 kg, $p < 0.001$; and 54.2 vs. 33.1 kg, $p < 0.001$, respectively), and with the difference in weight increasing with age due to a steeper type IV OI curve (Fig. **1c**). The mutant chain had a minimal effect on weight trajectories at 8 years old (20.5 vs. 17.0 kg, $p < 0.05$), but this distinction did not remain as children aged.

Head circumference of types III and IV OI does not differ by gender, type, or mutated collagen chain

Interestingly, the trajectories for growth of head circumference did not differ significantly by OI type, gender, or mutant collagen chain (Fig. **1d**).



Generation of standard OI curves

To generate standard OI growth curves, length and weight data were binned into half-year intervals. Each patient was limited to 1 data point per bin so that patients with frequent visits did not skew the curves. Standardized OI growth charts are presented in Supplementary Figures S1–S11, by OI type

Fig. 1 Comparison of composite longitudinal growth curves of children with types III and IV osteogenesis imperfecta (OI). (**a**) Comparison of longitudinal length curves by gender, OI type, and mutant collagen chain demonstrates that males are taller than females and children with type IV are taller than those with type III, while mutant type I collagen chain has no effect. (**b**) Comparison of longitudinal length curves by gender and OI type, gender and mutant collagen chain, and OI type and mutant collagen chain confirms the significant impact of OI type and lack of length correlation with specific mutant collagen chain. (**c**) Comparison of composite longitudinal weight curves by gender, OI type, and mutant collagen chain reveals significant impact of OI type. (**d**) Comparison of composite longitudinal curves of head circumference shows no impact of gender, OI type, or specific mutant collagen chain. For (**a**,**c**), * represents significant difference in length or weight, # represents significant difference in rate of increase. For length compared by gender and OI type in (**b**), * is significant difference in length between type III and IV females, ** is significant difference in rate of length increase between types III and IV OI females, # is significant difference between male and female type IV OI, ## is significant difference in rate of length increase between types III and IV males, *** is significant difference in rate of length increase between male and female type IV OI children. For length compared by OI type and mutant chain in (**b**), * and + represent significant difference in length and growth rate, respectively, between types III and IV OI children with pathogenic variants in *COL1A1*; • and ## represents significant differences in length and growth rate, respectively, between types III and IV OI children with pathogenic variants in *COL1A2*. Significance noted at $p < 0.05$.

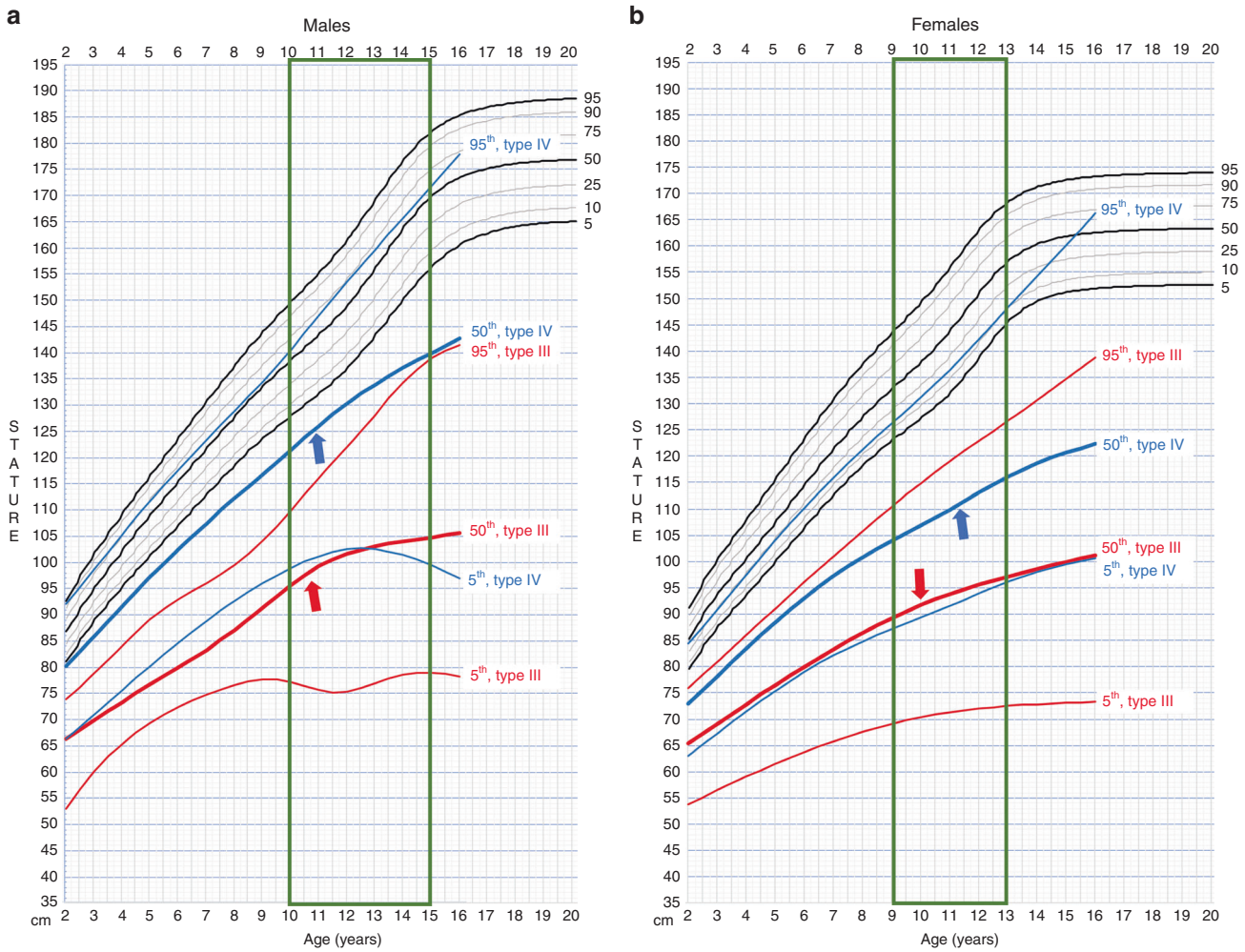


Fig. 2 Osteogenesis imperfecta (OI)-specific linear growth curves plotted against Centers for Disease Control and Prevention (CDC) growth curves for general US population. Growth charts for **a** males and **b** females. For both genders, the centile curves of types III (red) and IV (blue) overlap. The vertical box (green) highlights age range for pubertal growth spurt. Individuals with type III (red arrows) and IV (blue arrows) OI have blunted growth spurt.

and gender for length and weight. In addition, body mass index (BMI) values were calculated from length and weight data and the growth charts constructed for individual OI type and gender (Supplementary Figures S12–S16).

The median lengths of 2-year-old males and females with OI were 72.6 cm and 69.1 cm (*z*-scores: −4.25 and −4.65, respectively, versus the general population of children in the United States). The median lengths of 16-year-old males and females with OI were 124.4 cm and 112.8 cm (*z*-score: −5.55 and −7.77, respectively, versus US standard), respectively. The median weight of 2-year-old males and females were 8.54 and 8.13 kg (*z*-score: −3.86 and −4.34, respectively, versus US

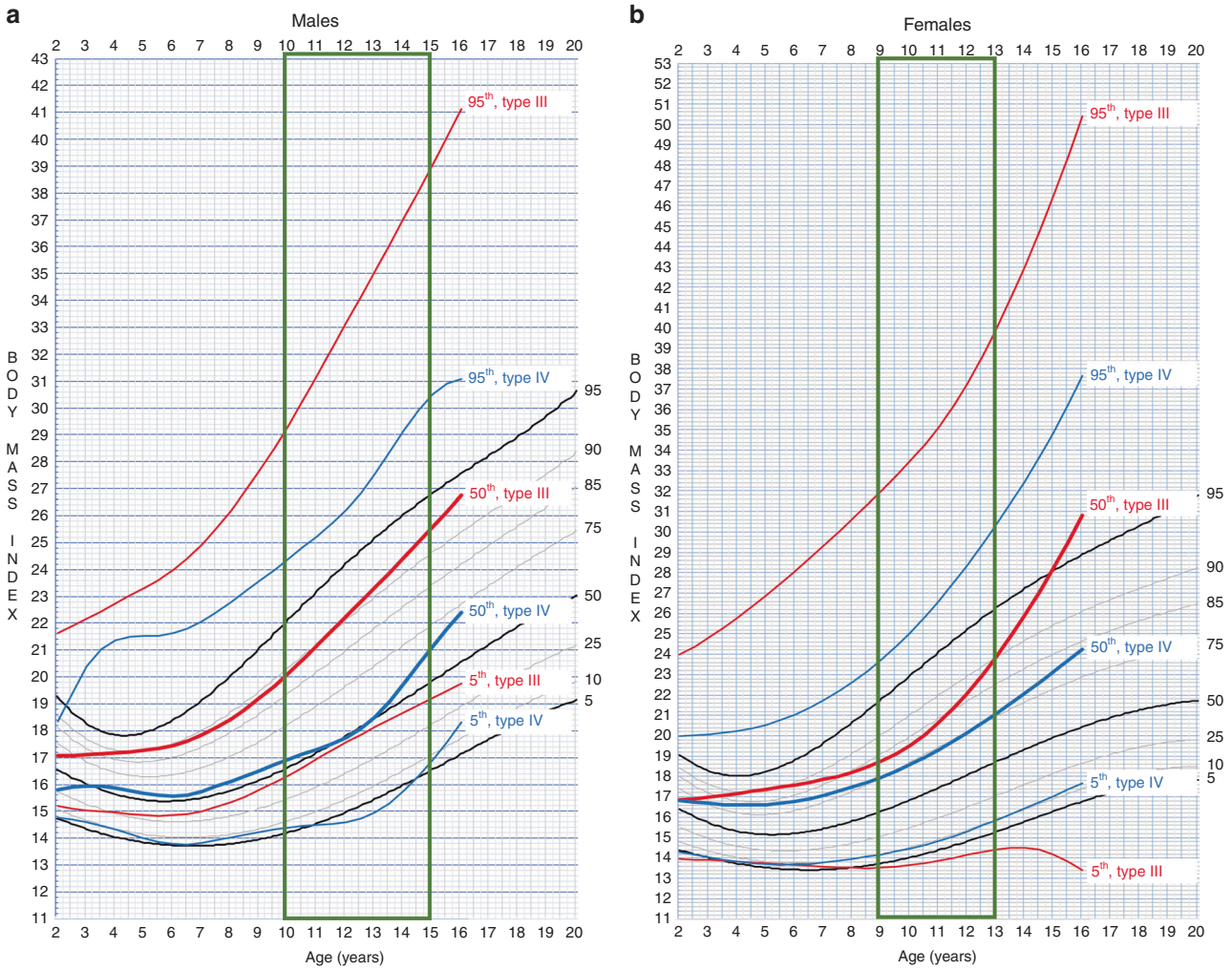


Fig. 3 Osteogenesis imperfecta (OI)-specific body mass index (BMI) growth curves plotted against Centers for Disease Control and Prevention (CDC) growth curves for general US population. Growth charts for (**a**) males and (**b**) females. Individuals with type III (red) have markedly higher BMI at all three centiles than those with type IV (blue) OI. The vertical box (green) highlights age range for pubertal growth spurt.

standard). At age 16 years, the mean weight for males and females was 33.4 kg (*z*-score: −4.51) and 35.3 kg (*z*-score: −3.65), respectively.

Comparison of OI-specific and general population length growth curves

Direct comparison of OI-specific curves with the CDC length curves for the general US population[11,12] are shown (Fig. 2). For both genders, there is overlap of the types III and IV OI centile curves. The type III OI 50th centile curve is similar to the type IV OI 5th centile. The tallest type III OI children (95th centile) are in the range of the average type IV OI children (50th centile). In both genders, the tallest type IV OI children (95th centile) have growth curves parallel to (females) or well into (males) the lower half of the general population curves. The OI length curves reflect a blunted pubertal growth spurt for both types as compared with the general population, with type III (red arrows) showing greater growth deceleration than type IV (blue arrows) OI individuals.[13]

Comparison of BMI growth curves

When plotted on the same scales and overlaid on CDC BMI curves, BMI curves in both genders for type III OI are markedly higher than corresponding type IV centile curves (Fig. 3). For example, type III OI 50th centile curve overlies the CDC 90th (Fig. 3**a**) and 85th−90th (Fig. 3**b**) centile curves; whereas, type IV OI 50th centile curve overlies the CDC 50th and 75th curves for males and females, respectively. This effect on BMI by OI type is most pronounced when considering the 95th centile growth curves in either gender.

Gender also contributes to differences in OI BMI growth curves. In males (Fig. 3**a**), type III curves for the 5th, 50th, and 95th centile all overlap with higher general population centile curves than those for type IV OI. The BMI slope of change in males with type III OI appears to be maintained from the pubertal period onward (Fig. 3**a**). The BMI slope of change in females continues to increase (Fig. 3**b**), resulting in higher 50th and 95th centile curves for females than males after age

12 years. For type IV OI, male BMI curves for the 50th and 95th centile track with the corresponding curves in the general population (Fig. 3a); whereas, female curves diverge upward after age 10 years starting with the 50th centile (Fig. 3b).

Overlapping of OI and the CDC general population BMI curves clearly demonstrates the presence of higher body mass index in a substantial proportion of individuals with OI (Fig. 3).

DISCUSSION

Significant growth deficiency is a cardinal feature of OI, but information on growth patterns in OI children has been sparse. The typical growth trajectories in types I, III, and IV OI[3] are not suitable for comparison with individual patients. Lund et al. assembled the first cross-sectional data on length and weight of 86 patients with types I, III, and IV OI, including children and adults.[14] They also separated patients into those with quantitative (OI type I) versus qualitative defects (OI types III and IV), although they did not distinguish between mutant collagen alpha chains. Type III/IV OI patients were found to be shorter than type I OI patients. Head circumference was increased above the general population but did not differ significantly among OI types. North American cross-sectional data on OI growth were assembled from the initial treatment visit of 125 children in a pamidronate treatment trial.[15] Types III and IV OI mean length curves were distinct and growth deficiency increased with severity of the dysplasia. Collagen pathogenic variantswere not analyzed. Most recently, cross-sectional data on 343 children and adults with OI[16] also supported increasingly impaired growth with more severe OI types.

The study presented here compares longitudinal growth data of 100 children with types III and IV OI and known collagen pathogenic variants. Composite growth curves compare length, weight, and head circumference in types III and IV OI. Stature in OI is significantly affected by gender (males are taller) and OI type (type III individuals are shorter), but not by mutant collagen chain. Weight trajectories differ only by OI type, reflecting the greater size of type IV children. Head circumference does not differ by gender, type, or mutant collagen chain, in agreement with Lund.[14] Although glycine substitutions are more likely to be lethal in *COL1A1* than *COL1A2*[2], the nonlethal substitutions in our patients do not have a chain-specific effect on length, weight, or head circumference.

OI-specific length, weight, and BMI curves derived from the longitudinal data reveal substantial overlap in centiles between types III and IV OI. Individuals with either OI type have a blunted pubertal linear growth spurt. Individuals with type III OI have significantly higher BMI when compared with the general population.

The longitudinal linear growth curves presented here reflect preponderantly the intrinsic growth deficiency of the axial skeleton in OI. Other skeletal factors, such as bowing of long bones, vertebral compressions, and scoliosis,[17] as well as popcorn formation at the metaphyses of long bones,[18] also make contributions to growth deficiency in OI. Anecdotal observations in the NIH natural history cohort suggest a correlation between decreased growth rate and increased scoliosis during puberty. Growth deficiency in OI is not due to defects in endocrine aspects of the growth hormone (GH) axis.[19] The growth responsiveness of many type IV OI children to administration of exogenous recombinant growth hormone (rGH)[20] suggests end-organ resistance may be contributory. Additionally, the BMI growth curves effectively demonstrate the presence of significant obesity in the OI population. The relative contributions of decreased activity secondary to recurrent fractures and decreased mobility, and of intrinsic cellular factors, remain to be determined. These OI-specific growth curves will fill an ongoing need in clinical care of patients with OI.

ELECTRONIC SUPPLEMENTARY MATERIAL

The online version of this article (https://doi.org/10.1038/s41436-018-0307-y) contains supplementary material, which is available to authorized users.

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DISCLOSURE

The authors declare no conflicts of interest.

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Supplementary Materials and Methods

Statistics

Differences in growth curves based on patient's gender, OI type (III vs. IV), and location of mutation (COL1A1 vs. COL1A2) were analyzed using non-linear multilevel growth modeling. Analyses estimated the sample average growth curves across age (years) and tested for population group differences in size (intercept), instantaneous growth rate (slope), and curvature (non-linearity) or acceleration of the growth curves. Separate growth curves were analyzed for the three growth parameters: length, weight, and head circumference.

First, for each growth parameter, data for each patient were reviewed to identify and correct likely errors. Next, growth parameter-by-age scatterplots for each patient were visually examined to determine an appropriate model form that could be applied to the individual patient growth curves. From the visual inspection we decided to fit a quadratic growth curve to the data set. The multilevel growth models were fit using maximum likelihood estimation (MLE) with the nlme package from the R[1] environment for statistical computing (MacOS). Females, Type III, and COL1A1 were coded as reference groups.

Multilevel modeling was deemed appropriate because it accommodates for the longitudinal and unbalanced structure of the data, the latter arising from patients varying in the number and timing of their measurements (see **Supplementary Table S1**). For example, for the 99 children that had measures for length, the number of measurement occasions ranged from 1 to 40 visits, and the time interval between occasions ranged from 0 to 8.44 years (a 0-year interval occurred when children had only 1 visit). Additionally,

the median age of the child at the initial assessment was 2.2 years (range = 1.67 to 14.97 years), and median age at last assessment was 14.3 years (range = 2.1 to 17.5 years). Multilevel modeling is not limited to balanced data because it fits the growth model to each patient's set of scores and the resulting growth coefficients for the intercept, slope, and curvature serve as the dependent variables for higher-level analyses.

Data were structured in two levels, with level 1--the lowest unit of analysis--patient's scores across measurement occasions (within subjects), nested within level 2--individual patients. The Level 1 submodel modeled quadratic growth across time with age (years) and age^2 as predictor variables (see equation 1):

$$Y_{ti} = \pi_{0i} + \pi_{1i}Age_{ti} + \pi_{2i}Age_{ti}^2 + e_{ti} \qquad [1]$$

where Y_{ti} represents the predicted size at age t years (e.g., t = 2, 2.5, 3, . . ., k_i) for child i (i.e., i = 1, . . . ,99); π_{0i} is the intercept or status (size) of child i at age t; π_{1i} is the instantaneous slope or growth rate of child i at age t; π_{2i} captures the curvature or acceleration in child i's growth trajectory, and e_{ti} is the residual for child i at age t. Acceleration is defined as the change in slope over time. The coefficient π_{2i} indicates both the shape (concave or convex) and steepness of the growth curve. A positive coefficient indicates a convex curve (vertex is at a minimum and curve opens upward) and a negative coefficient indicates a concave curve (vertex is at a maximum and curve opens downward). The steepness of the curve increases as the absolute value of the magnitude of the coefficient increases.

The Level-2 submodel modeled the Level-1 regression coefficients--intercept, age, and age^2 (equations 2 - 4, respectively)-- as random (varying) effects with gender, OI type, and mutation location as predictor variables (X_i):

$$\pi_{0i} = \beta_{00} + \beta_{01}X_i + r_{0i} \qquad [2]$$

$$\pi_{1i} = \beta_{10} + \beta_{11}X_i + r_{1i} \quad [3]$$

$$\pi_{2i} = \beta_{20} + \beta_{21}X_i + r_{2i} \quad [4]$$

The composite multilevel model formed by combining equations 1-4 was:

$$Y_{ti} = \beta_{00} + \beta_{01}X_i + \beta_{10}Age_{ti} + \beta_{11}(X_i \times Age_{ti}) + \beta_{20}Age_{ti}^2 + \beta_{21}(X_i \times Age_{ti}^2) + r_{0i} + r_{1i}Age_{ti} + r_{2i}Age_{ti}^2 + e_{ti} \quad [5]$$

where β_{00} is the population average for the level-1 intercepts for patients in the reference group (e.g., females), β_{01} is the population average difference between the intercepts of the reference and non-reference groups (e.g., males); β_{10} is the population average of the level-1 slopes (growth rate or rate of change) for persons in the reference group, and β_{11} is the population average difference between the slopes of the reference and non-reference groups; β_{20} is the population average of the acceleration for persons in the reference group, and β_{21} is the population average difference in acceleration between the reference and non-reference group; r_{0i}, r_{1i}, and r_{2i}, represent a difference between the average population values and a patient's unique value for the intercept, slope, and acceleration, respectively; and e_{ti} represents the within patient error (Singer & Willett, 2003, p 53, Table 3.2)[2].

Generally, the intercept captures the initial status or size at 0 years of age. Since 0 years was not a meaningful reference point for the estimated growth curves, Age was recentered by subtracting 2 years (Age - 2) from age at every measurement occasion. Recentered Age improved the interpretability of the coefficients to capture patient's size and instantaneous growth rate at 2 years of age.

For quadratic growth models, acceleration (the coefficient for Age^2) is a characteristic of the entire growth curve--it remains constant across the age range (see **Supplementary tables S4a - 4c**), but the initial status, π_{0i}, and instantaneous rate of

growth, π_{2i}, depend on the particular choice of age at assessment (Raudenbush & Bryk, 2002, p 169)[3]. Likewise, the population differences in initial status, β_{01}, and instantaneous rate of growth, β_{11}, change across age. The age-dependent coefficients are easily calculated by refitting the growth curves using Age recentered to the desired age. We demonstrated how the values of the intercept ($\beta_{00}, \beta_{01}, \beta_{02}$), and slope ($\beta_{10}, \beta_{11}$) change across the age span by refitting the models with Age centered at ages 8 years (Age - 8) and 16 years (Age - 16).

Standard growth curve construction

Smoothed centile curves across age were constructed using the GAMLSS (generalized additive model for location, scale, and shape[4]) package from R[1]. GAMLSS was adopted by the World Health Organization (WHO) to develop their 2007 growth reference charts,[5, 6] and incorporates the LMS method[7,8] of curve smoothing used by the CDC to develop their 2000 growth charts.[9]

Data were binned into half-year intervals, with the lowest bin at 1.5 years as the lowest bin and 17.5 years. as the highest bin. Age bins covered a range of $\pm$ .25 years. Each patient was limited to one score per age bin per growth parameter. When patients had multiple assessments within the same half-year interval, the occasion that fell closest to the defined age bin or which provided the most complete information (i.e., had scores for the most growth parameters) was retained for analysis. As a result, a total of 305 measurement occasions for 66 patients (range = 1 to 14, median = 4, M = 4.62, SD = 3.04) were dropped.

Centile curves were constructed using the LMS method[7] and an extension of it developed by Rigby and Stasinopoulos[4]. Briefly, these methods assume that the growth

variable, *Y* (e.g., length), rather than having a normal distribution as typically assumed, is distributed as one of several non-normal distributions: the Box-Cox Cole Green (BCCGo), a truncated standard normal distribution; the Box-Cox power exponential (BCPEo), a truncated exponential power distribution, and the Box-Cox t (BCTo), a truncated t distribution. The GAMLSS model is represented as

$$Y \sim D(\mu, \sigma, \nu, \tau)$$

$$g1(\mu) = h1(x)$$

$$g2(\sigma) = h2(x)$$

$$g3(\nu) = h3(x)$$

$$g4(\tau) = h4(x)$$

$$x = \text{age}^{\xi}$$

where Y~D() represents Y distributed as one of the three distributions described above, and the distribution defined by its median (μ), approximate coefficient of variation (σ), the Box-Cox power needed to correct for skewness (ν), and kurtosis (τ). The BCCGo distribution is defined by only the first three parameters (μ, σ, ν); whereas the BCPEo and BCTo distributions are defined by all four parameters (μ, σ, ν, τ). The g() functions represent link functions (e.g., the identity or natural log functions), the h() functions represent non-parametric smoothing functions, and ξ is an optional power transformation of Age that may make it easier to fit the smoothing curve. For our analyses the smoothing functions, h(age), were penalized piecewise cubic b-splines, also known as p-splines. The smoothness of p-splines is defined by its effective degrees of freedom (e*df*). GAMLSS uses an iterative process and maximum likelihood to determine a distribution, the appropriate degrees of freedom for the distribution parameters (μ, σ, ν, τ), and ξ.

Overlay growth curves construction

Linear and BMI growth data for the general population 2-20 years of age was downloaded from the Center for Disease Control and Prevention (CDC) website (https://www.cdc.gov/growthcharts/percentile_data_files.htm. Accessed July 25, 2018). Data from the CDC and this manuscript were plotted in Excel using same axes scales, and the graphs overlapped.

Results

Multilevel longitudinal analyses

Supplementary **Tables S3a** to **S3c** report the model deviances and Likelihood Ratio Chi-square tests for length, weight, and head circumference, respectively. Tables display the results of fitting the null model (no predictors, e.g., **Table S3a**, model 0), the level-1 individual quadratic growth model (Age and Age^2 included in model, e.g., **Table S3a**, model 1), and several level-2 models that show the univariate and multivariate relations of Type, Gender, and Collagen chain to growth status and change (e.g., **Table S3a** models 2 - 9). The tables also show the results of fitting a maximum model and the minimal adequate model (MAM).[10] The maximum model (e.g., **Table S3a**, model 9) includes all the possible main, two-way and three-way interactions of the level 1 and level 2 predictors. The minimal adequate model (e.g., **Table S3a**, model 8) produces the smallest residual deviance with the constraint that all the regression terms are statistically significant. When the MAM contains interactions, the necessary lower order terms are included in the model even if not statistically significant. The deviance is a measure of how well the current

model fits the sample data relative to a general model that fits the data perfectly. Because adding predictor variables to the model decreases the deviance, the Akakie's Information Criterion (AIC), and the Bayesian Information Criterion (BIC) were developed to adjust or "penalize" the deviance for model complexity under the assumption that simpler models are better. For all three fit indices, a smaller value indicates a better fitting model. Models were estimated using full maximum likelihood so that a Likelihood Ratio Chi-square test could be used to test improvement in fit for increasingly complex nested models (e.g., model 1 vs model 2). The AIC and BIC were used to compare non-nested models (e.g., model 2 vs model 3). The results reported in the **Tables S3a** to **S3c** are the same irrespective of how Age and Age^2 were centered because centering changes the location but not the shape of the distribution along the Age axis. That is to say, models centering the analysis at two years, Age-2 and $(Age-2)^2$, and eight years old, Age-8 and $(Age-8)^2$, produce the same Deviance, AIC, BIC, and LR Chi-square values. However, the values of the coefficients for the intercept and spontaneous rate of change (slope) do differ depending on centering (see **Supplementary Table S4**).

The quadratic growth models fit the data significantly better than the null models for length, weight, and head circumference (**Supplementary Tables S3a** to **S3c**, respectively, model comparisons 0 v 1). Furthermore, models that allowed the coefficients of the linear (Age) and quadratic (Age^2) growth terms to vary across individual patients fit significantly better than models holding them constant (ps < .0001; not shown in **Supplemental Table S3**).

Length

The curvature of the growth curves for Length was concave and shallow, reflective of an acceleration coefficient of -0.08 (**Supplementary Table S4a**). There was a statistically significant interaction between type and gender (**Supplementary Table S3a**, model 5). The interaction model significantly reduced the residual deviance compared to a model with Type alone (LR chi-square (6) = 13.825, p = .0316). The minimal adequate model (model 8) indicated that interactions involving the acceleration term (Type x Age^2, Gender x Age^2, and Type x Gender x Age^2) could be eliminated without significantly altering the fit (LR chi-square (4) = 0.521, p = .9714). The simpler interaction model produced the lowest AIC (7227.03) and BIC (7306.87) values.

Fitting the minimal adequate model (model 8) with data centered at 2, 8, and 16 years shows that as patients grow older the difference in average length between Type III and Type IV patients and the difference in average length between females and males increases and becomes more variable. Furthermore, the effect of type is more prominent than the effect of gender (**Supplementary Table S4a**). Since type and gender were scaled the same (0, 1), the larger effect of type is demonstrated by the size of the coefficients for β_{01} and β_{02}, holding constant the effect of the other across the age range. For example, the difference between Type IV females and Type III females was 6.95 cm, 22.38 cm, and 42.94 cm for 2-, 8-, and 16-year olds respectively. In contrast, the difference between Type III males and Type III females was -.86 cm, 4.01 cm, and 10.51 cm for the three ages, respectively. Increased variation in Length with age is shown in the values for the random effects of the intercept (r_0). The standard deviation in patient length was 6.512 cm, 12.738

cm, and 25.902 cm for 2-year, 8-year, and 16-year olds respectively. The average rate of change (slope) in length decreases across time (**Supplementary Table S4**). For Type III females, the slopes were 3.24 cm/yr, 2.31 cm/yr, and 1.06 cm/yr at 2 years, 8 years and 16 years, respectively. Again, type had a larger effect than gender on rate of change. The slopes were 2.57 cm/yr greater for Type IV females, but only .81 cm/year greater for Type III males. The effects of type and gender on the slope were constant across the age range because the interaction terms of type and gender with Age^2 (e.g., Type x Age^2) were not included in the minimal adequate model (compare, for example Age x Type for Length in Table S4a with Age x Type for Weight in **Table S4b**). In summary, controlling for gender, Type IV patients were longer and had steeper growth curves than Type III patients across the age span. Type IV males were taller and had steeper growth curves than Type IV females across the age span. In contrast, Type III males and females had similar lengths in the early years, but the steeper slopes of the males resulted in Type III males being significantly longer than Type III females in the later teen years. Modeling multiple growth spurts would have required at the least a cubic growth model.

There was no consistent difference in length associated with collagen chain when it was the only predictor variable in the model (**Supplementary Table S3a**, model 4), nor when it was included as a covariate with type (**Supplemental Table S3a**, models 6 & 9) or gender (**Supplemental Table S3a**, models 7 & 9).

Weight

The curvature of the growth curves for Weight was convex and shallow, reflective of an acceleration coefficient of 0.09 (**Supplemental Table S4b**). Only OI type

(**Supplemental Table S3b**, model 2) significantly reduced the residual deviance compared to the individual growth model (model 1 vs 2, LR chi-square (3) = 13.825, p = .0316). Additionally, model 2 was the minimal adequate model. Although the Maximum Model (model 9) significantly reduced the residual deviance relative to model 2 (LR chi-square (18) = 30.034, p = .0371), the combination of significant and non-significant interaction terms in the equation made interpreting the results challenging. Additionally, the AIC and BIC values of the maximal model were larger compared to the OI type model. The difference in the average weight of Type IV and Type III patients increased across the age span: 2.12 kg, 6.91 kg, and 21.06 kg at 2 years, 8 years and 16 years, respectively, with Type IV patients significantly heavier at each of the ages. The rate of change also was greater for Type IV patients than Type III patients. Although rate of change was not significantly different at 2 years (difference = 0.38, p = .127), the difference was significantly greater for Type IV patients at 8 years (difference = 1.21, p < .0001) and 16 years (difference = 2.32, p = .0004).

Head Circumference

The curvature of the growth curves for head circumference was concave and shallow as indicated by an acceleration coefficient of -0.02 (**Supplemental Table S4c**). The minimal adequate model was the unconditional quadratic model (**Supplemental Table S3c**, model 1). Neither type, gender, nor collagen chain, either singly (models 2-4) or jointly (models 2-8), had a statistically significant association with head circumference. The average head circumference for the sample grew from 48.08 cm at age 2 years to 55.51 cm at age 16 years. The rate of change declined across the age span (0.79 cm/yr at age 2

years to 0.27 cm/year at age 16 years. The variability of the intercept (r_0) and the rate of change (r_1) changed little across the age span.

Evaluating Model Assumptions

Two basic distributional assumptions underlie multilevel analyses: 1) within-group residuals (level-1) and the random effects (level-2) are normally distributed, and 2) the within-group residuals and random effects have equal variances at each level of the predictors. Typically these assumptions are assessed using diagnostic scatter plots of the residuals, the fitted values, and the estimated random effects. The assumptions were checked for the minimal adequate models for each growth parameter: model 8 for length (**Tables S3a and S4a**), model 2 for weight (**Tables S3b and S4b**), and model 1 for head circumference (**Tables S3c and S4c**). The diagnostic plots for the three models suggested that the assumptions were met.

Standardized Growth Curves

Smoothed centile curves across age for length were constructed using the Box-Cox Power Exponential distribution with a log link for the median parameter (BCPEo), and for weight using the Box-Cox Cole and Green distribution with a log link for the median parameter (BCCGo). Metric BMI values (kilograms/squared meters) were computed from patients' weight and length values based on the following formula:

$$\frac{\text{weight (kg)}}{\left(\frac{\text{length (cm)}}{100}\right)^2}$$

Since length was recorded as centimeters, values had to be divided by 100 to convert them to meters. Smoothed centile curves for metric BMI across age were constructed using the BCPEo distribution. **Figures S1 to S3** and **S12** show the data points and superimposed smoothed centile curves for the 5th, 25th, 50th, 75th, and 95th centiles from 2 years to 16 years for length, weight, and BMI. **Figure S1** allows a visual comparison of the length-for-age curves for females (top row) and males (bottom row) constructed with OI types III and IV combined (left column) and for OI types III (column 2) and IV (column 3) separately. Weight-for-age centile curves for each gender are also presented (right column). Weight-for-age curves for females separated by OI type are presented in **Figure S2**, and for males separated by type in **Figure S3**. **Figure S12** provides a visual comparison of BMI-for-age centile curves for gender by OI type. Single page growth curves without data points for each gender by OI type group are given in **Figures S4** to **S11** and **S13** to **S16**: length-for-age for females (**S4-S5**), length-for-age for males (**S6-S7**), weight-for-age for females (**S8-S9**), weight-for-age for males (**S10-S11**), BMI-for-age for females (**S13-S14**), and BMI-for-age for males (**S15-S16**).

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Supplemental Tables

Table S1. NICHD Pediatric OI Longitudinal Cohort

		COL1A1	*COL1A2*	Total Patients	Observations
Type III	Male	13	5	18	811
	Female	17	10	27	1286
	Total	**30**	**15**	**45**	**2097**
Type IV	Male	16	11	27	912
	Female	11	17	28	1371
	Total	**27**	**28**	**55**	**2283**
Total		**57**	**43**	**100**	**4380**

Table S2a. Number of Measurement Occasions and Time Interval Between Visits

Growth Parameter	N Patients	Total Observations	Observations /child				Interval between visits (yrs)			
			Range	Median	Mean	SD	Range	Median	Mean	SD
Length	99	1480	1 to 40	15.0	14.95	10.04	0 to 6.54	.45	.55	.51
Weight	98	1502	1 to 40	15.5	15.33	10.16	0 to 6.54	.45	.56	.54
Head circ	99	1398	1 to 40	13.0	14.12	10.27	0 to 8.44	.44	.52	.43

Table S2b. Summary of Patients' Age at First and Last Visit

Growth Parameter	Age first visit (yrs)				Age last visit (yrs)			
	Range	Median	Mean	SD	Range	Median	Mean	SD
Length	1.67 to 14.97	2.23	4.07	3.43	2.06 to 17.52	14.33	12.46	4.48
Weight	1.67 to 14.97	2.22	4.08	3.45	2.06 to 17.52	14.37	12.56	4.40
Head circ	1.67 to 14.97	2.20	4.02	3.43	2.00 to 17.52	14.33	12.40	4.58

Table S3a. Length (cm): Model Deviances and Comparisons

Model #	Description	Fixed Effects Terms	*df*	Deviance	AIC	BIC	Model Comparisons Models	*df*	LR Chi	*p*
	Level 1									
0	Null	I	3	12361.05	12367.05	12383.02				
1	Individual quadratic growth	I, A, A^2	10	7273.83	7293.83	7347.05	0 v 1	7	5087.225	**<.0001**
	Level 2									
2	Type	I, A, A^2, T, TxA, TxA^2	13	7210.34	7236.34	7305.53	1 v 2	3	63.490	**<.0001**
3	Gender	I, A, A^2, G, GxA, GxA^2	13	7266.44	7292.44	7361.63	1 v 3	3	7.389	0.0605
4	Collagen chain	I, A, A^2, C, CxA, CxA^2	13	7271.89	7297.89	7367.08	1 v 4	3	1.940	0.5850
5	Type + Gender	I, A, A^2, T, G, TxG, TxA, GxA, TxGxA, TxA^2, GxA^2, $TxGxA^2$	19	7196.51	7234.51	7335.64	2 v 5	6	13.825	**0.0316**
6	Type + Collagen chain	I, A, A^2, T, C, TxC, TxA, CxA, TxCxA, TxA^2, CxA^2, $TxCxA^2$	19	7207.02	7245.02	7346.15	2 v 6	6	3.320	0.7677
7	Gender + Collagen chain	I, A, A^2, G, C, GxC, GxA, CxA, GxCxA, GxA^2, CxA^2, $GxCxA^2$	19	7258.26	7296.26	7397.39	3 v 7	6	8.177	0.2254
8	Minimal Adequate Model (MAM)	I, A, A^2, T, G, TxG, TxA, GxA	15	7197.03	7227.03	7306.87	5 v 8	4	0.521	0.9714
9	Maximum Model	I, A, A^2, T, G, C, TxG, TxC, GxC, TxGxC, TxA, GxA, CxA, TxGxA, TxCxA, GxCxA, TxGxCxA, TxA^2, GxA^2, CxA^2, $TxGxA^2$, $TxCxA^2$, $GxCxA^2$, $TxGxCxA^2$	31	7184.33	7246.33	7411.33	8 v 9	16	12.704	0.6942

I = Intercept, A=centered age (Age-2), T = OI Type, G = Gender, C = Collagen chain
LR Chi = Likelihood Ratio Chi Square, AIC = Akaike's Information Criterion, BIC = Bayesian Information Criterion
MAM = Minimal Adequate Model

Table S3b. Weight (kg): Model Deviances and Comparisons

Model #	Description	Fixed Effects Terms	*df*	Deviance	AIC	BIC	Model Comparisons Models	*df*	LR Chi	*p*
	Level 1									
0	Null	I	3	11276.90	11282.91	11298.92				
1	Individual quadratic growth	I, A, A^2	10	6123.12	6143.12	6196.49	0 v 1	7	5153.788	**<.0001**
	Level 2									
2	Type (MAM)	I, A, A^2, T, TxA, TxA^2	13	6095.59	6121.59	6190.97	1 v 2	3	27.530	**<.0001**
3	Gender	I, A, A^2, G, GxA, GxA^2	13	6119.16	6145.16	6214.54	1 v 3	3	3.952	0.2667
4	Collagen chain	I, A, A^2, C, CxA, CxA^2	13	6116.76	6142.76	6212.14	1 v 4	3	6.354	0.0956
5	Type + Gender	I, A, A^2, T, G, TxG, TxA, GxA, TxGxA, TxA^2, GxA^2, $TxGxA^2$	19	6083.99	6121.99	6223.39	2 v 5	6	11.601	0.0715
6	Type + Collagen chain	I, A, A^2, T, C, TxC, TxA, CxA, TxCxA, TxA^2, CxA^2, $TxCxA^2$	19	6089.25	6127.25	6228.65	2 v 6	6	6.338	0.3864
7	Gender + Collagen chain	I, A, A^2, G, C, GxC, GxA, CxA, GxCxA, GxA^2, CxA^2, $GxCxA^2$	19	6103.94	6141.94	6243.34	2 v 7	6	8.351	0.2135
8	Maximum Model	I, A, A^2, T, G, C, TxG, TxC, GxC, TxGxC, TxA, GxA, CxA, TxGxA, TxCxA, GxCxA, TxGxCxA, TxA^2, GxA^2, CxA^2, $TxGxA^2$, $TxCxA^2$, $GxCxA^2$, $TxGxCxA^2$	31	6065.55	6127.55	6293.00	2 v 8	18	30.034	**0.0371**

I = Intercept, A=centered age (Age - 2) , T = OI Type, G = Gender, C = Collagen chain
LR Chi = Likelihood Ratio Chi Square, AIC = Akaike's Information Criterion, BIC = Bayesian Information Criterion
MAM = Minimal Adequate Model

Table S3c. Head Circumference (cm): Model Deviances and Comparisons

Model #	Description	Fixed Effects Terms	*df*	Deviance	AIC	BIC	Model Comparisons Models	*df*	LR Chi	*p*
	Level 1									
0	Null	I	3	6406.65	6412.65	6428.45				
1	Individual quadratic growth (MAM)	I, A, A^2	10	3850.66	3870.66	3923.33	0 v 1	7	2555.988	**<.0001**
	Level 2									
2	Type	I, A, A^2, T, TxA, TxA^2	13	3845.85	3871.85	3940.31	1 v 2	3	4.811	0.1862
3	Gender	I, A, A^2, G, GxA, GxA^2	13	3848.08	3874.08	3942.54	1 v 3	3	2.589	0.4595
4	Collagen chain	I, A, A^2, C, CxA, CxA^2	13	3845.16	3871.16	3939.62	1 v 4	3	5.504	0.1384
5	Type + Gender	I, A, A^2, T, G, TxG, TxA, GxA, TxGxA, TxA^2, GxA^2, $TxGxA^2$	19	3840.68	3878.68	3978.74	2 v 5	6	5.171	0.5220
6	Type + Collagen chain	I, A, A^2, T, C, TxC, TxA, CxA, TxCxA, TxA^2, CxA^2, $TxCxA^2$	19	3840.34	3878.34	3978.40	2 v 6	6	5.513	0.4798
7	Gender + Collagen chain	I, A, A^2, G, C, GxC, GxA, CxA, GxCxA, GxA^2, CxA^2, $GxCxA^2$	19	3839.83	3877.83	3977.88	2 v 7	6	6.026	0.4203
8	Maximum Model	I, A, A^2, T, G, C, TxG, TxC, GxC, TxGxC, TxA, GxA, CxA, TxGxA, TxCxA, GxCxA, TxGxCxA, TxA^2, GxA^2, CxA^2, $TxGxA^2$, $TxCxA^2$, $GxCxA^2$, $TxGxCxA^2$	31	3828.40	3890.40	4053.65	1 v 8	21	22.263	0.3845

I = Intercept, A=centered age (Age-2), T = OI Type, G = Gender, C = Collagen chain
LR Chi = Likelihood Ratio Chi Square, AIC = Akaike's Information Criterion, BIC = Bayesian Information Criterion
MAM = Minimal Adequate Model

Table S4a. Coefficients of Minimal Adequate Model for Length (cm)

Model 8 from Table S3a	Age 2 years			Age 8 years			Age 16 years		
Fixed Effects	**Coef.**	**s.e.**	**p-value**	**Coef.**	**s.e.**	**p-value**	**Coef.**	**s.e.**	**p-value**
Intercept, β_{00} Average length Type III females	66.66	1.3331	< 0.0001[a]	83.30	2.328	< 0.0001[a]	96.78	4.458	< 0.0001[a]
Type, β_{01} ***Type IV*** females - ***Type III*** females	6.95	1.866	0.0003[b]	22.38	2.919	< 0.0001[b]	42.94	5.079	< 0.0001[b]
Gender, β_{02} Type III ***males*** - Type III ***females***	-0.86	2.050	0.6771[b]	4.01	3.040	0.1897[b]	10.51	5.152	0.0441[b]
Type x Gender, β_{03} (Type III females + Type IV males) - (Type IV females + Type III males)	6.50	2.768	0.021[b]	6.50	2.768	0.021[b]	6.50	2.768	0.021[b]
Slope, Age, β_{10} Average Rate of Change Type III females cm/year	3.24	0.282	< 0.0001[a]	2.31	0.268	< 0.0001[a]	1.06	0.404	0.0087[a]
Age x Type, β_{11} ***Type IV*** females - ***Type III*** females	2.57	0.307	< 0.0001[a]	2.57	0.307	< 0.0001[a]	2.57	0.307	< 0.0001[a]
Age x Gender, β_{12} Type III ***males*** - Type III ***females***	0.81	0.307	0.0083[a]	0.81	0.307	0.0083[a]	0.81	0.307	0.0083[a]
Acceleration*, Age^2, β_{20} Average Type III females	-0.08	0.015	< 0.0001[a]	-0.08	0.015	< 0.0001[a]	-0.08	0.015	< 0.0001[a]
Random Effects	**s.d.**			**s.d.**			**s.d.**		
Within person variation, *e*	1.873			1.873			1.873		
Between person variation									
Intercept, r_0: Average Length	6.512			12.738			25.902		
Slope, r_1: Rate of Change	1.643			1.501			2.837		
Acceleration, r_2	0.119			0.119			0.119		

Table note: s.e. = standard error; s.d. = standard deviation. [a] degrees of freedom = 1411; [b] degrees of freedom = 95; *Acceleration (rate of change in the slope) indicates the direction and steepness of the curve. Positive = upwards or convex, negative = downwards or concave. Curves grow steeper (narrower) as absolute values increase.

Table S4b. Coefficients of Minimal Adequate Model for Weight (kg)

Model 2 from Table S3b	Age 2 years			Age 8 years			Age 16 years		
Fixed Effects	**Coef.**	**s.e.**	**p-value**	**Coef.**	**s.e.**	**p-value**	**Coef.**	**s.e.**	**p-value**
Intercept, β_{00}									
Average Weight Type III	7.98	0.404	< 0.0001[a]	14.61	0.996	< 0.0001[a]	33.13	3.451	< 0.0001[a]
Type, β_{01}									
Type IV - Type III	2.12	0.568	0.0003[b]	6.91	1.331	< 0.0001[b]	21.06	4.573	< 0.0001[b]
Slope, Age, β_{10}									
Average Rate of Change Type III	0.59	0.184	0.0015	1.62	0.209	< 0.0001[a]	3.01	0.495	< 0.0001[a]
Age x Type, β_{11}									
Type IV - Type III	0.38	0.250	0.1268	1.21	0.277	< 0.0001[a]	2.32	0.658	0.0004
Acceleration*, Age^2, β_{20}									
Average Type III	0.09	0.020	< 0.0001[a]	0.09	0.020	< 0.0001[a]	0.09	0.020	< 0.0001[a]
Age^2 x Type, β_{21}									
Type IV - Type III	0.07	0.027	0.0116	0.07	0.027	0.0116	0.07	0.027	0.0116
Random Effects	**s.d.**			**s.d.**			**s.d.**		
Within person variation, *e*	1.296			1.296			1.296		
Between person variation									
Intercept, r_0: Average Weight	2.303			6.282			20.631		
Slope, r_1: Rate of Change	1.038			1.253			2.833		
Acceleration, r_2	0.114			0.114			0.114		

Table note: s.e. = standard error; s.d. = standard deviation. [a] degrees of freedom = 1434; [b]degrees of freedom = 96; *Acceleration (rate of change in the slope) indicates the direction and steepness of the curve. Positive = upwards or convex, negative = downwards or concave. Curves grow steeper (narrower) as absolute values increase.

Table S4c. Coefficients of Minimal Adequate Model for Head Circumference (cm)

Model 1 from Table S3c	Age 2 years			Age 8 years			Age 16 years		
Fixed Effects	**Coef.**	**s.e.**	**p-value**	**Coef.**	**s.e.**	**p-value**	**Coef.**	**s.e.**	**p-value**
Intercept, β_{00} Average Head Circumference (cm)	48.08	0.467	< 0.0001[a]	52.15	0.380	< 0.0001[a]	55.51	0.420	< 0.0001[a]
Slope, Age, β_{10} Average Rate of Change (cm)	0.79	0.043	< 0.0001[a]	0.57	0.017	< 0.0001[a]	0.27	0.040	< 0.0001[a]
Acceleration*, Age^2, β_{20} Average	-0.02	0.003	< 0.0001[a]	-0.02	0.003	< 0.0001[a]	-0.02	0.003	< 0.0001[a]
Random Effects	**s.d.**			**s.d.**			**s.d.**		
Within person variation, *e*	0.725			0.725			0.725		
Between person variation									
Intercept, r_0: Average Weight	4.518			3.734			4.002		
Slope, r_1: Rate of Change	0.311			0.117			0.263		
Acceleration, r_2	0.019			0.019			0.019		

Table note: s.e. = standard error; s.d. = standard deviation. [a] degrees of freedom = 1330; *Acceleration (rate of change in the slope) indicates the direction and steepness of the curve. Positive = upwards or convex, negative = downwards or concave. Curves grow steeper (narrower) as absolute values increase.

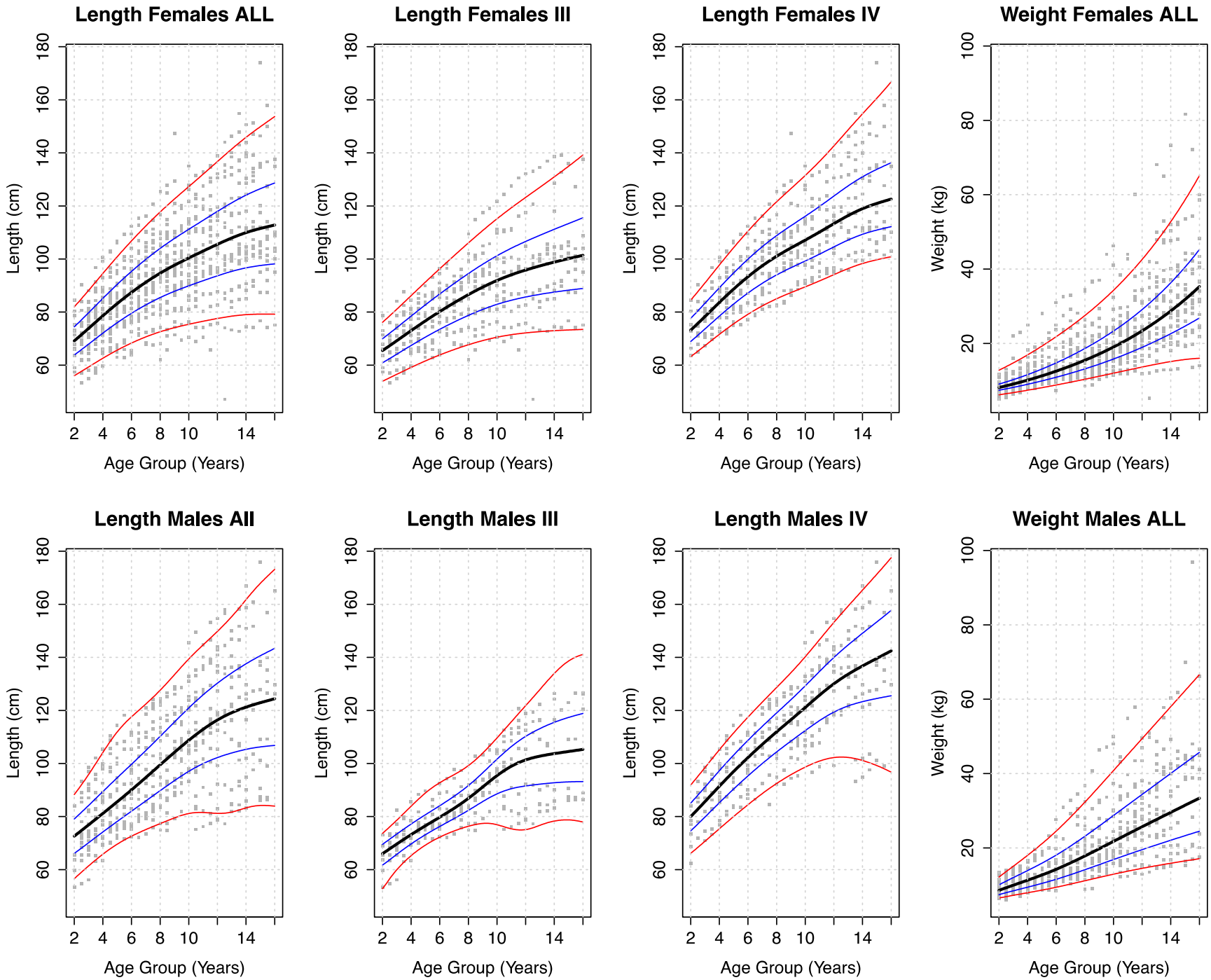

Figure S1: Longitudinal standard curves for length and weight of children with types III and IV OI. All data points used are displayed on the graphs.

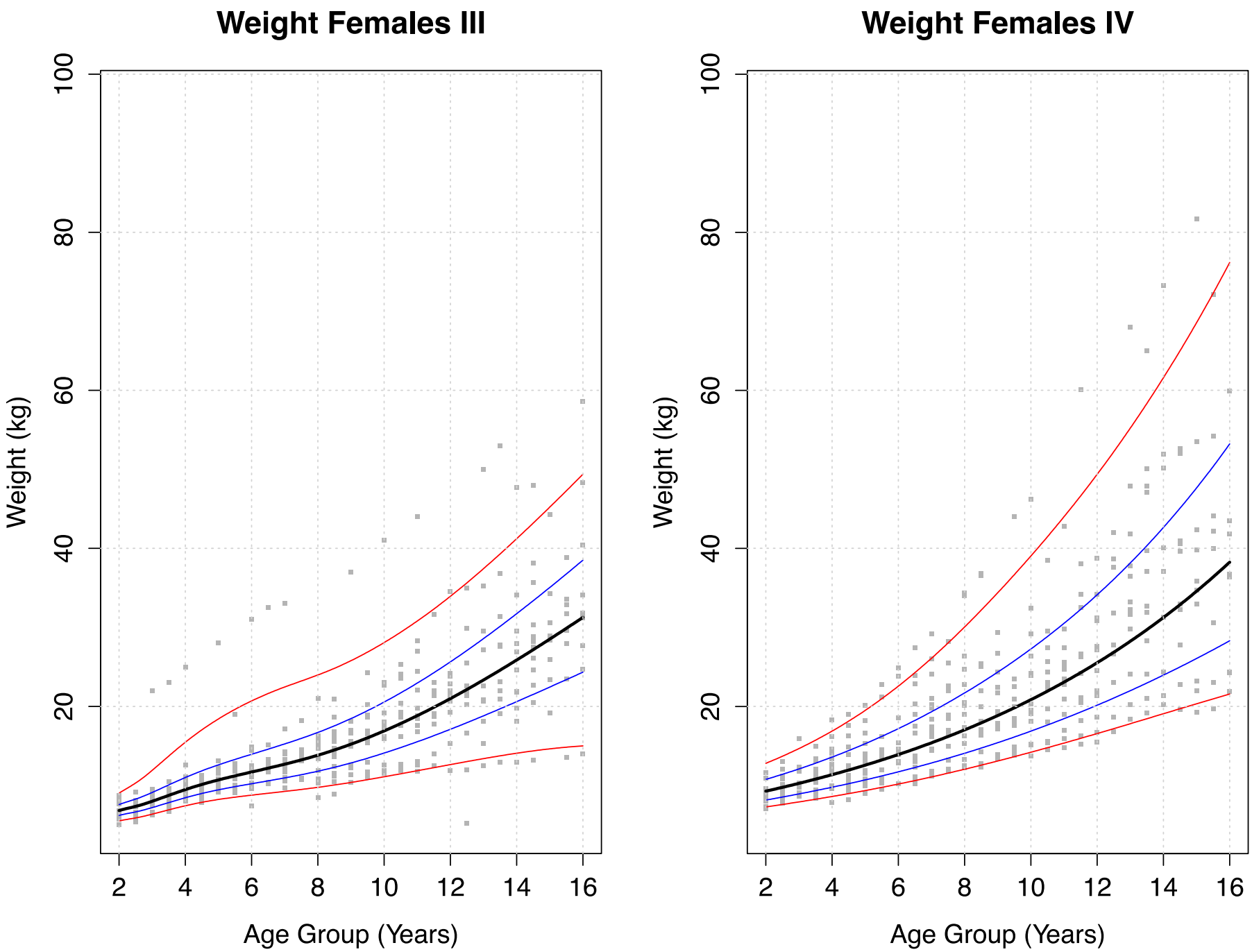

Figure S2: Longitudinal standard curves for weight of females with types III and IV OI. All data points used are displayed on the graphs.

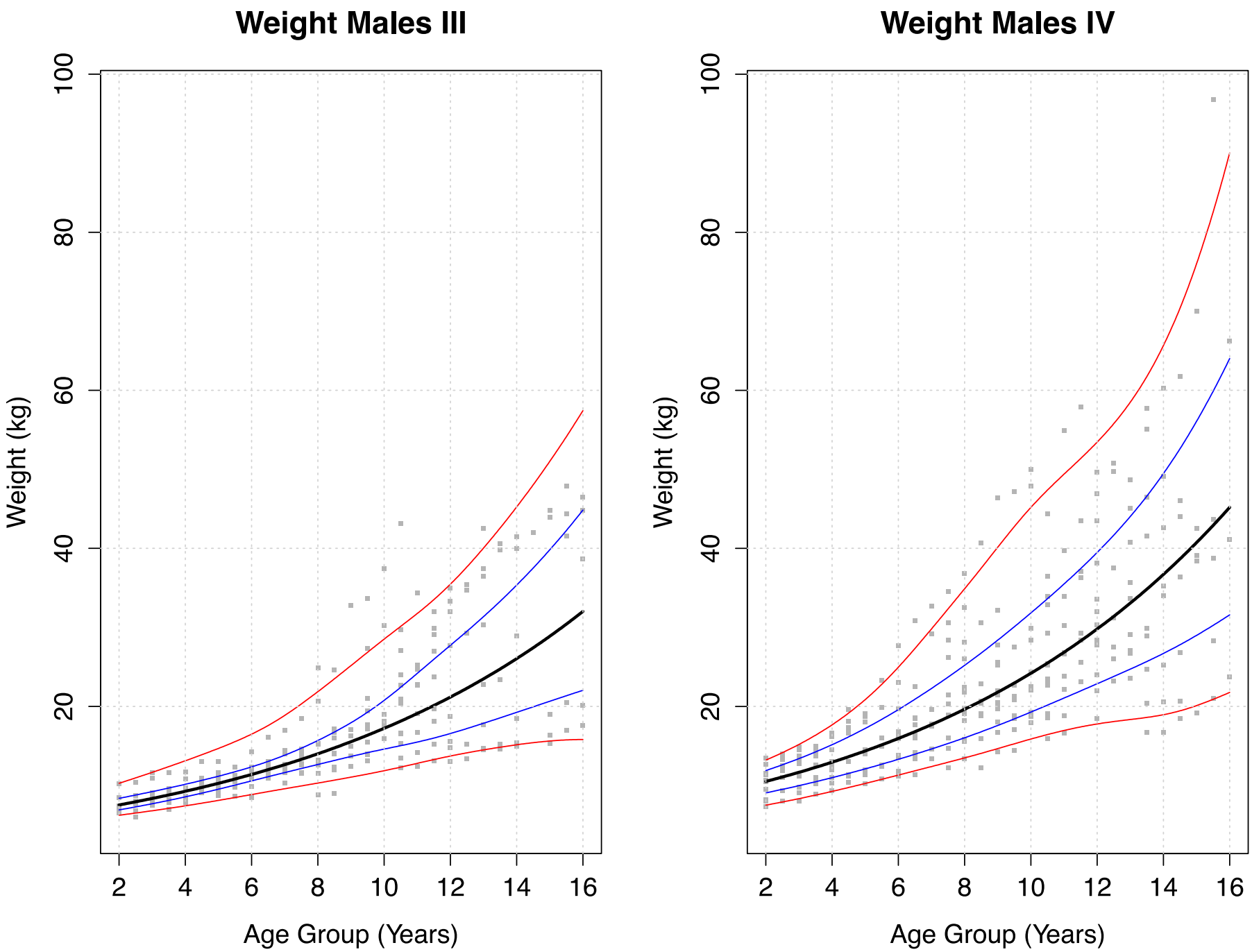

Figure S3: Longitudinal standard curves for weight of males with types III and IV OI. All data points used are displayed on the graphs.

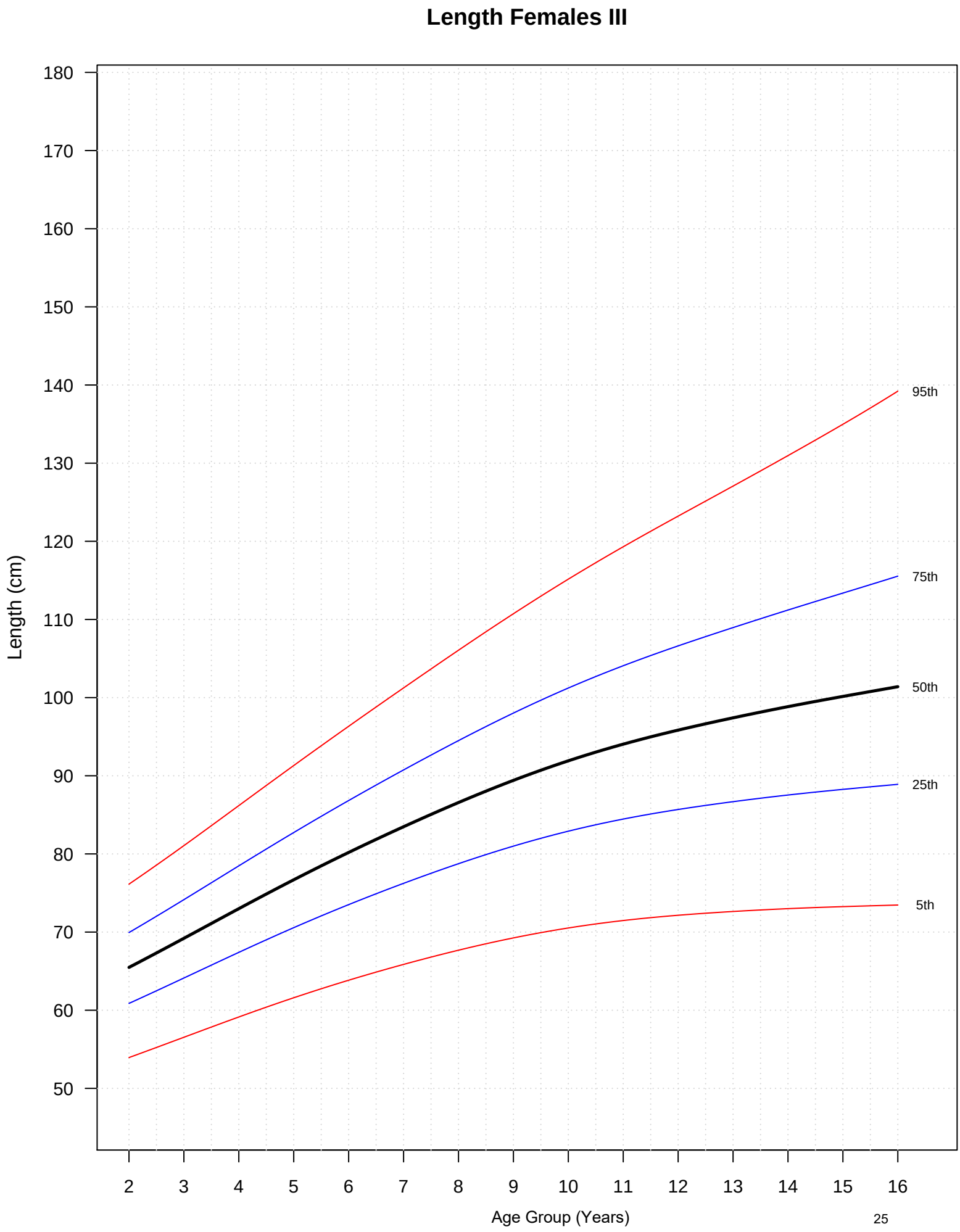

Figure S4: Longitudinal growth curves for length of females with type III OI.

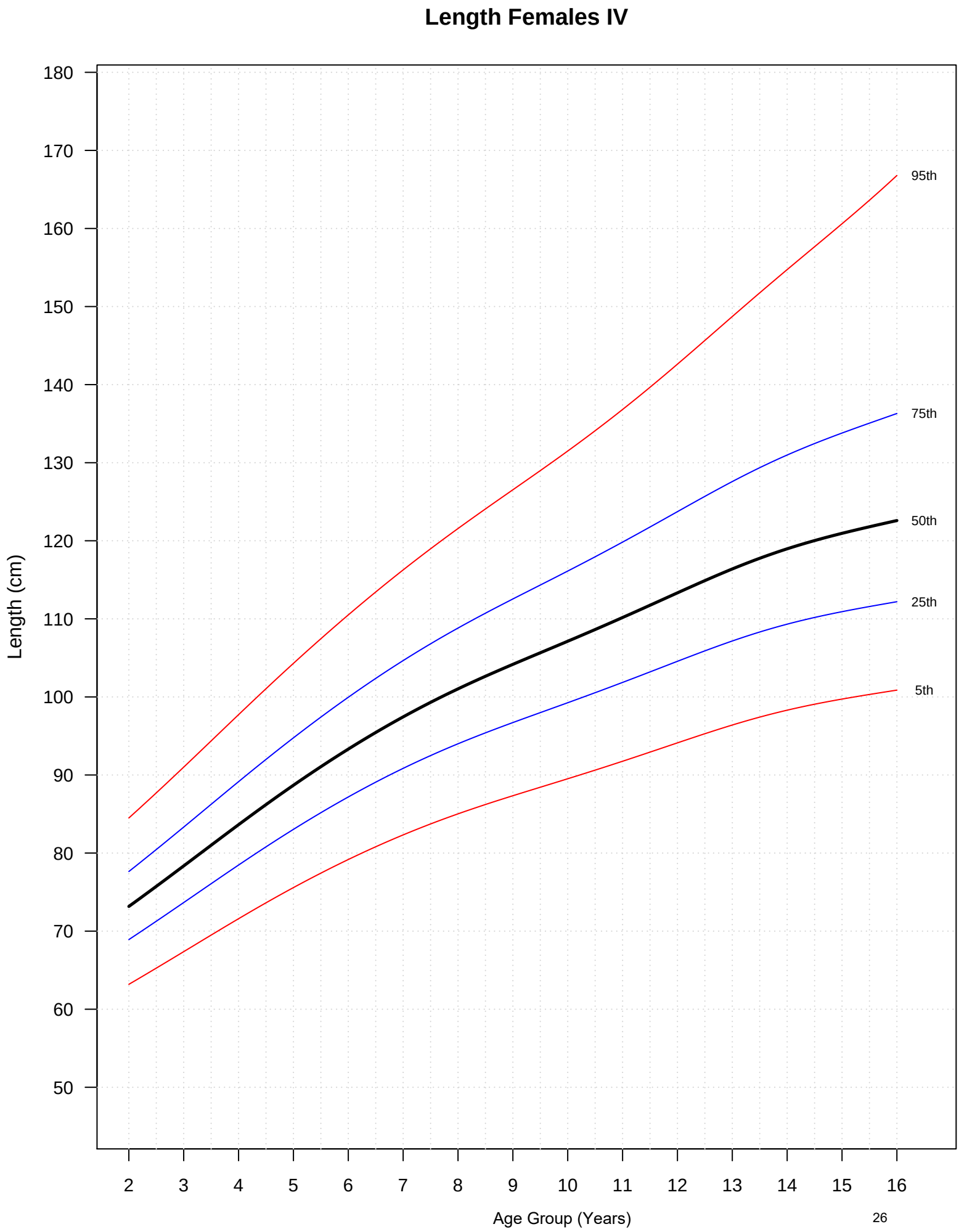

Figure S5: Longitudinal growth curves for length of females with type IV OI.

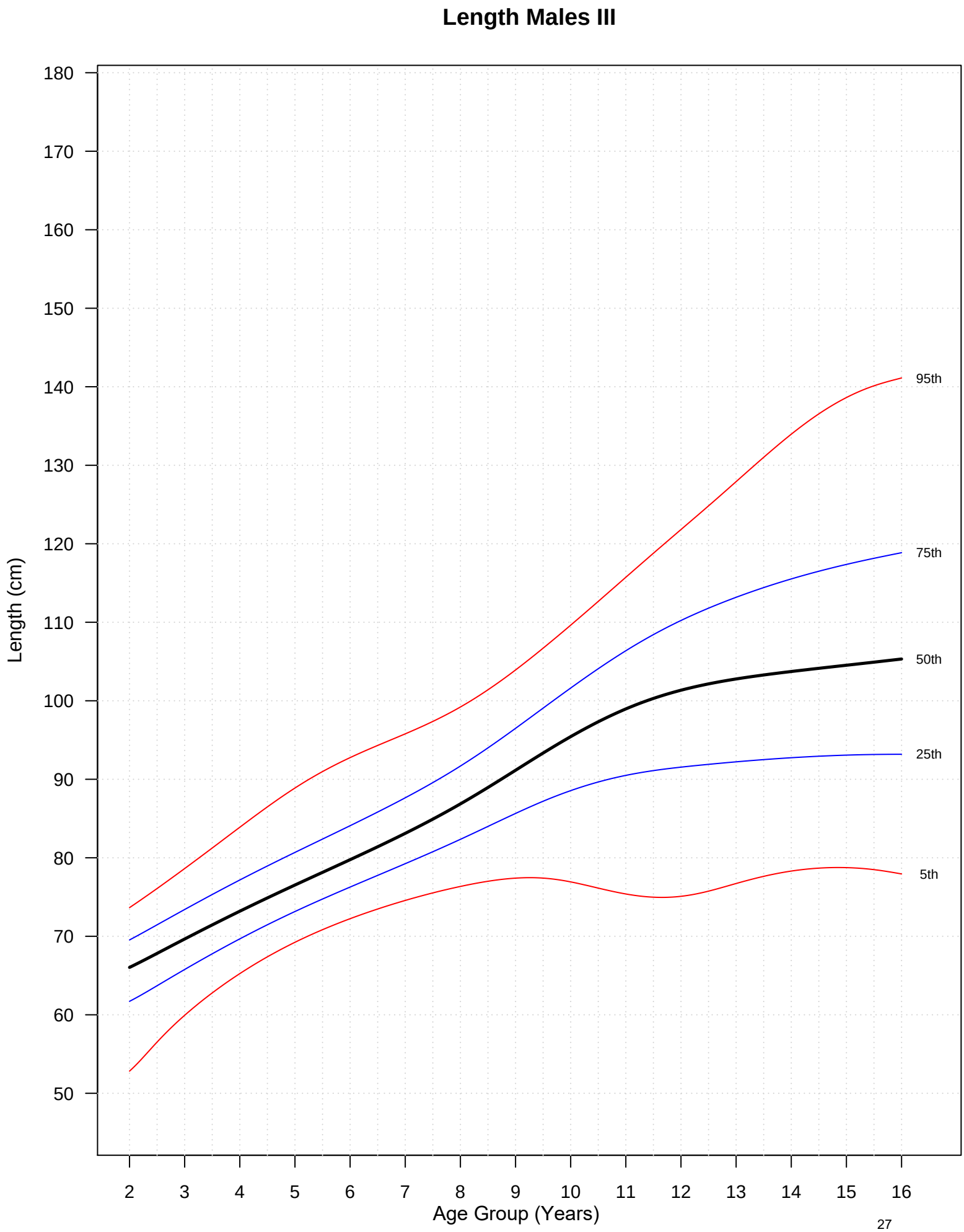

Figure S6: Longitudinal growth curves for length of males with type III OI.

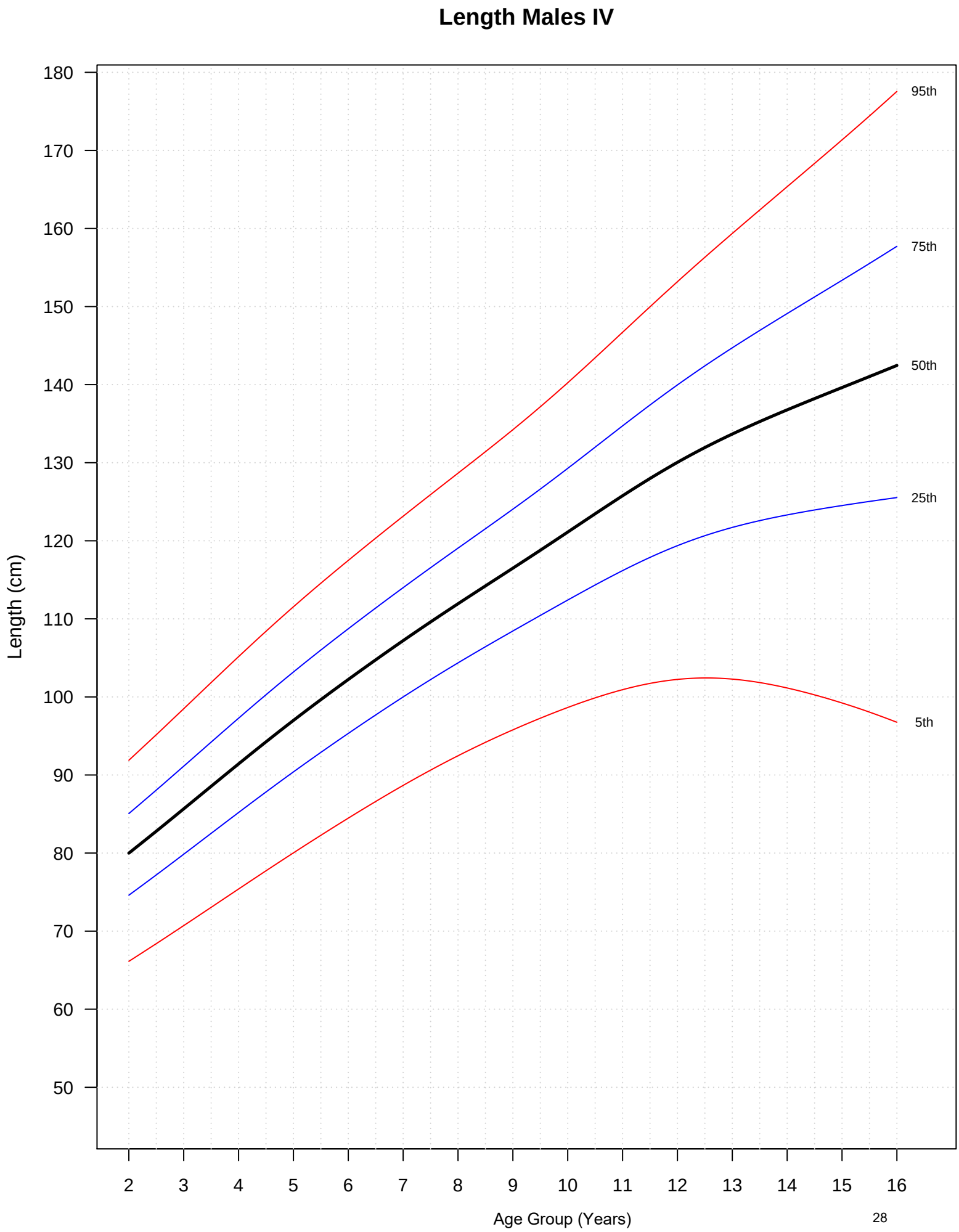

Figure S7: Longitudinal growth curves for length of males with type IV OI.

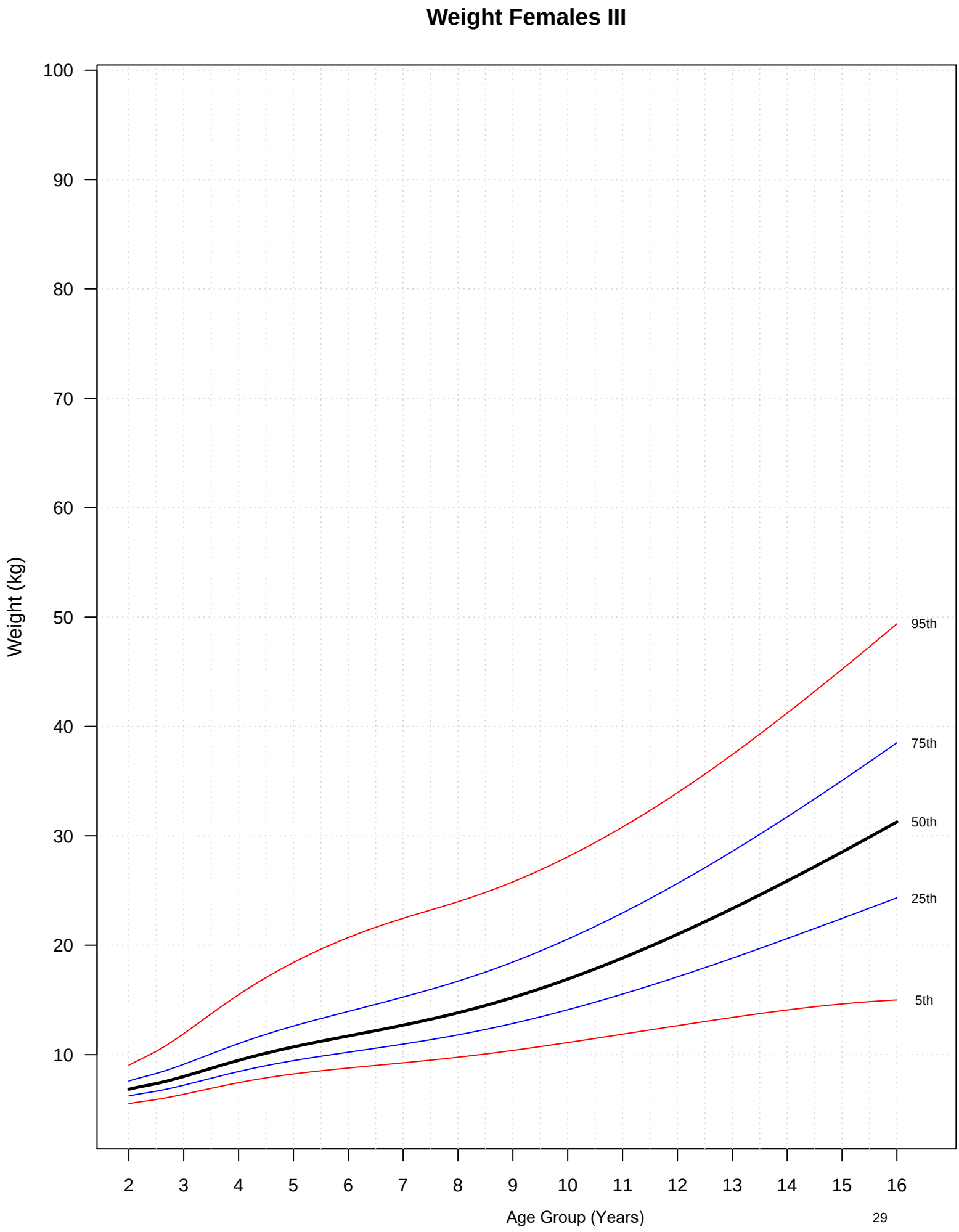

Figure S8: Longitudinal growth curves for weight of females with type III OI.

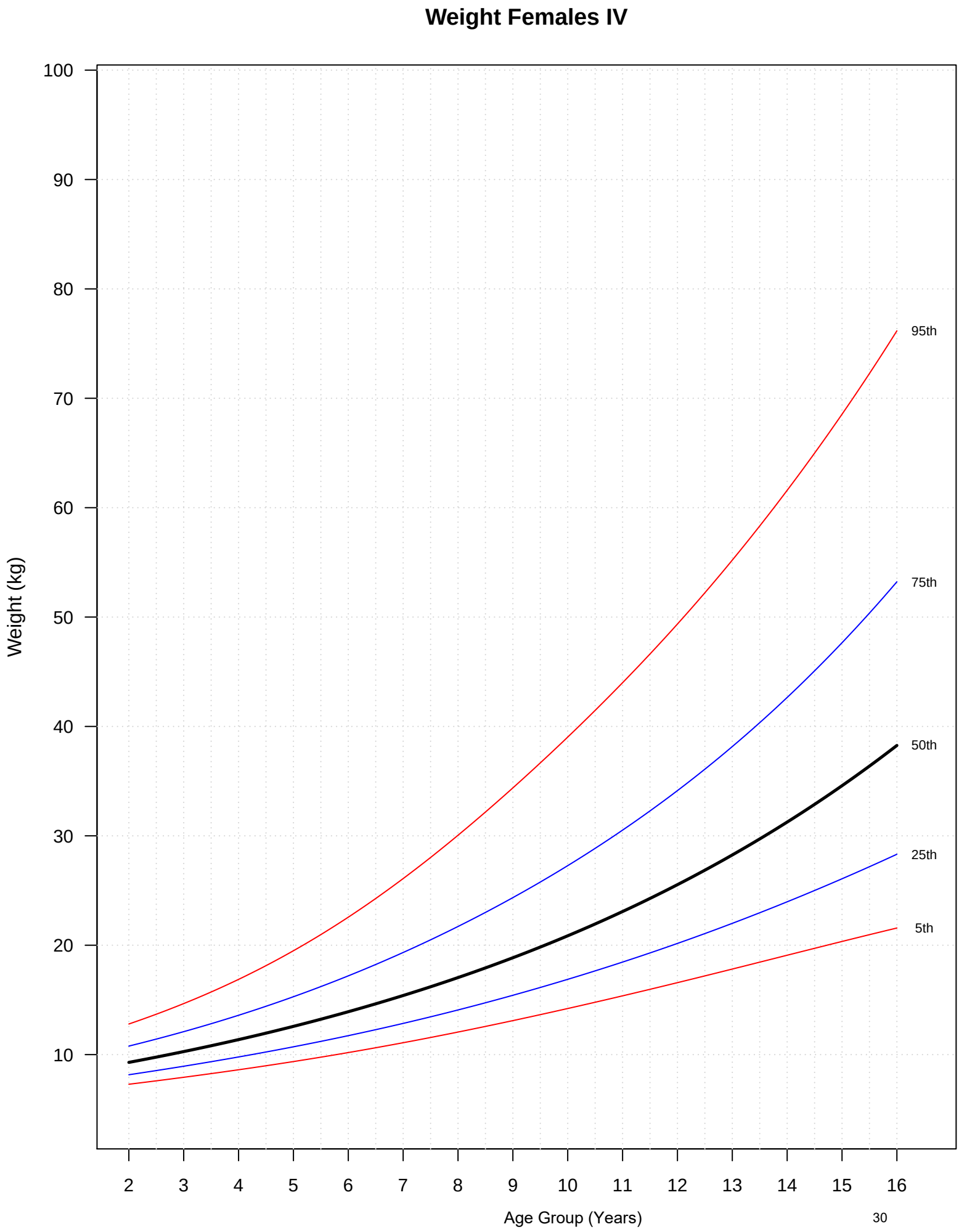

Figure S9: Longitudinal growth curves for weight of females with type IV OI.

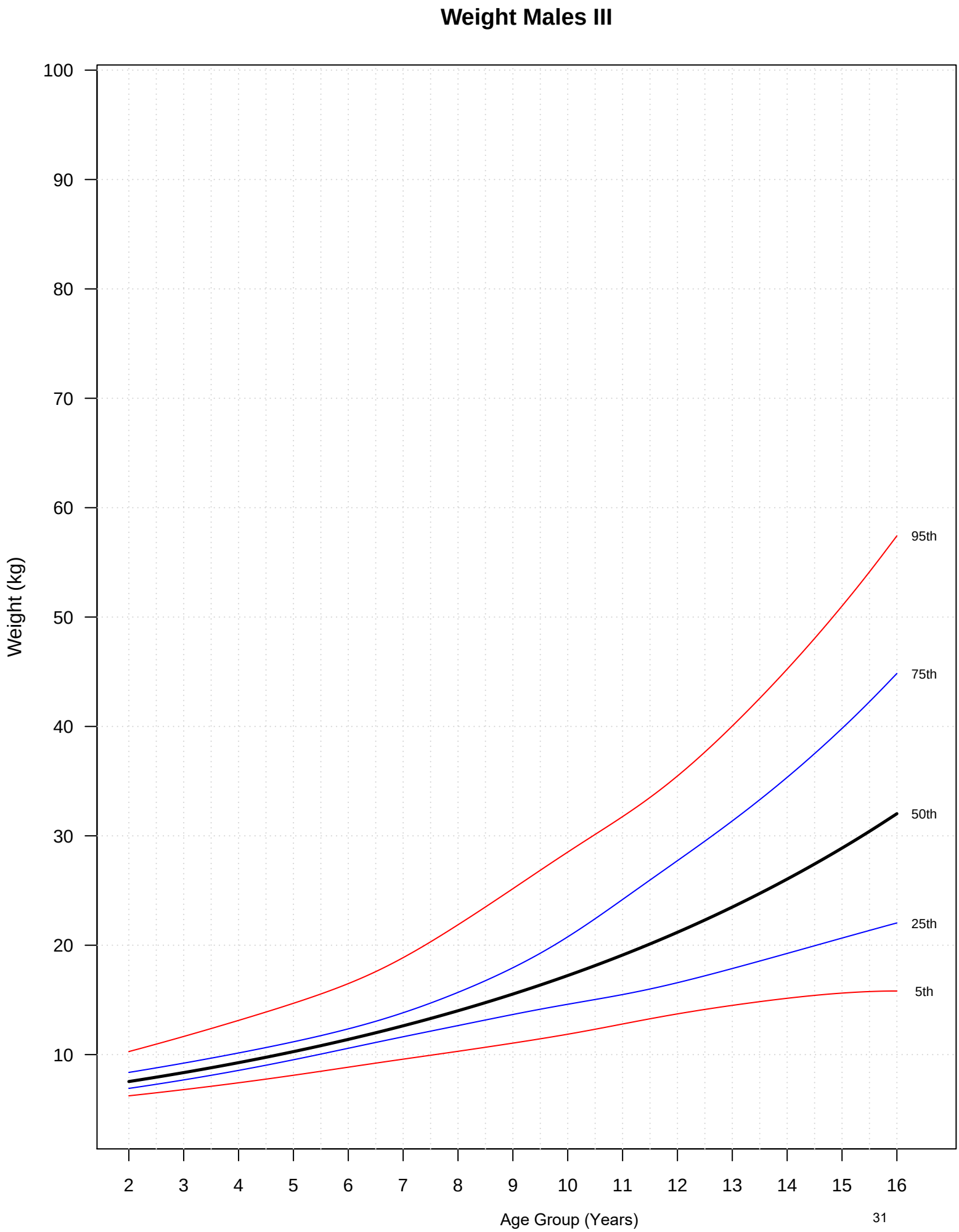

Figure S10: Longitudinal growth curves for weight of males with type III OI.

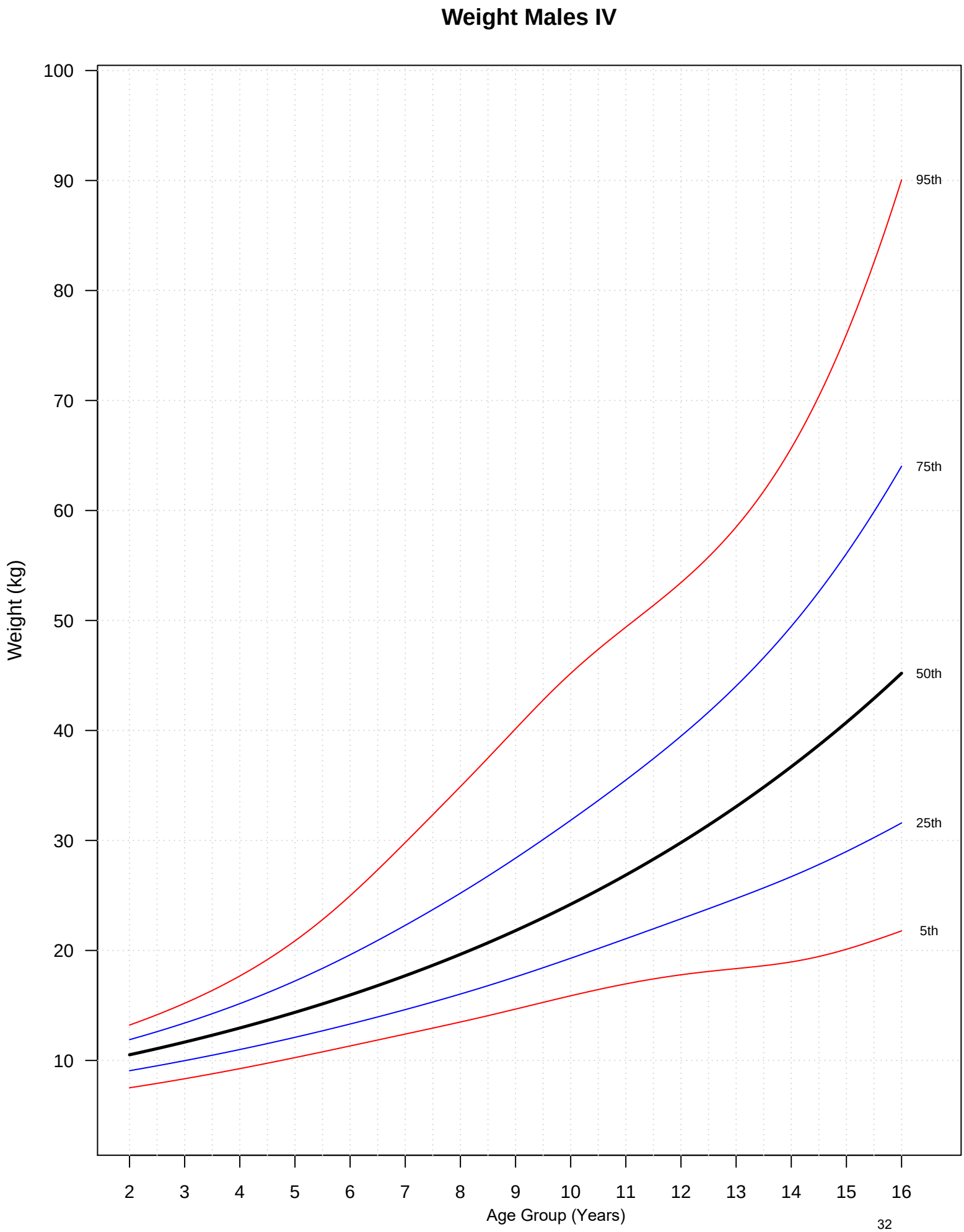

Figure S11: Longitudinal growth curves for weight of males with type IV OI.

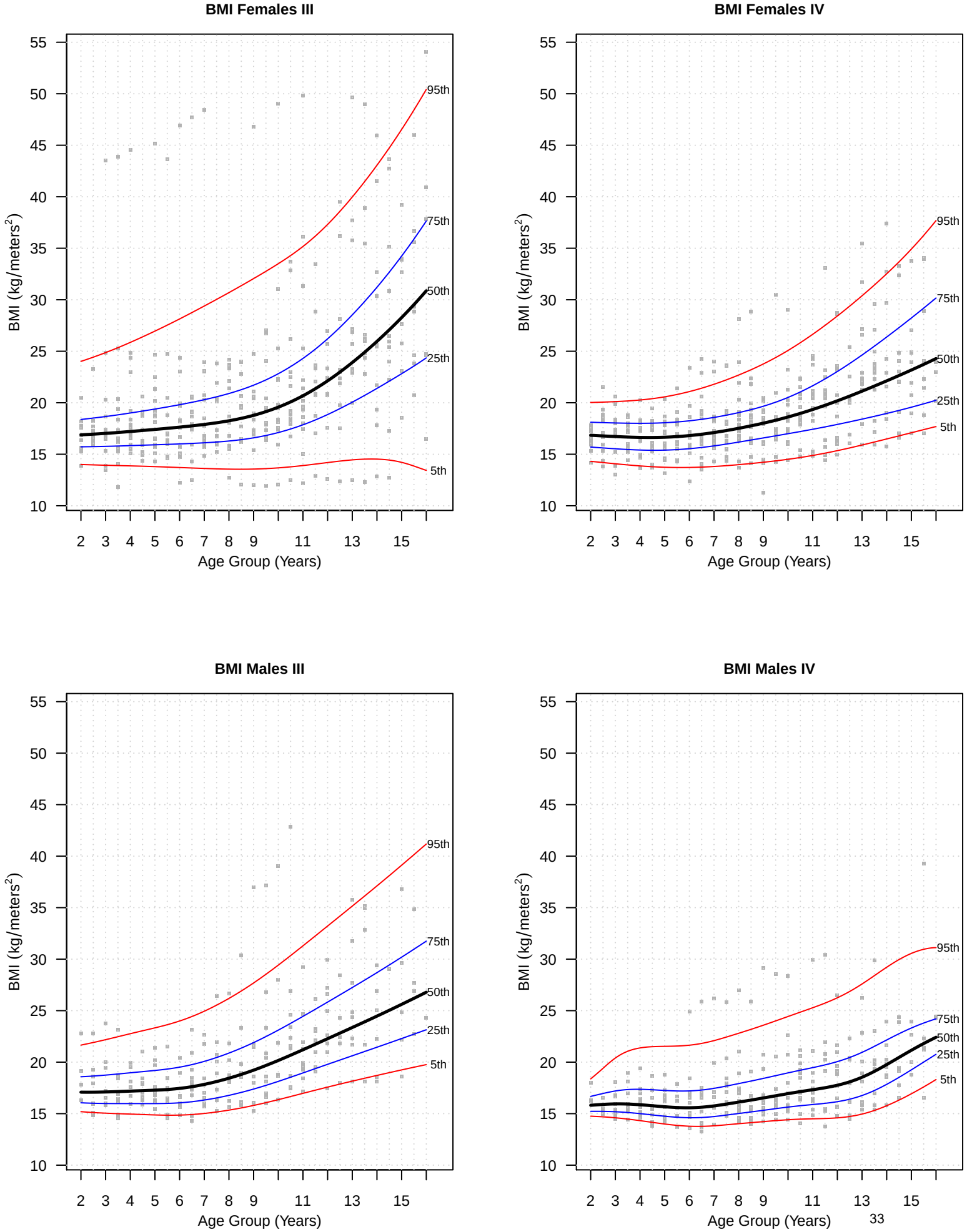

Figure S12: Longitudinal standard curves for BMI of females and males with types III and IV OI. All data points used are displayed on the graphs.

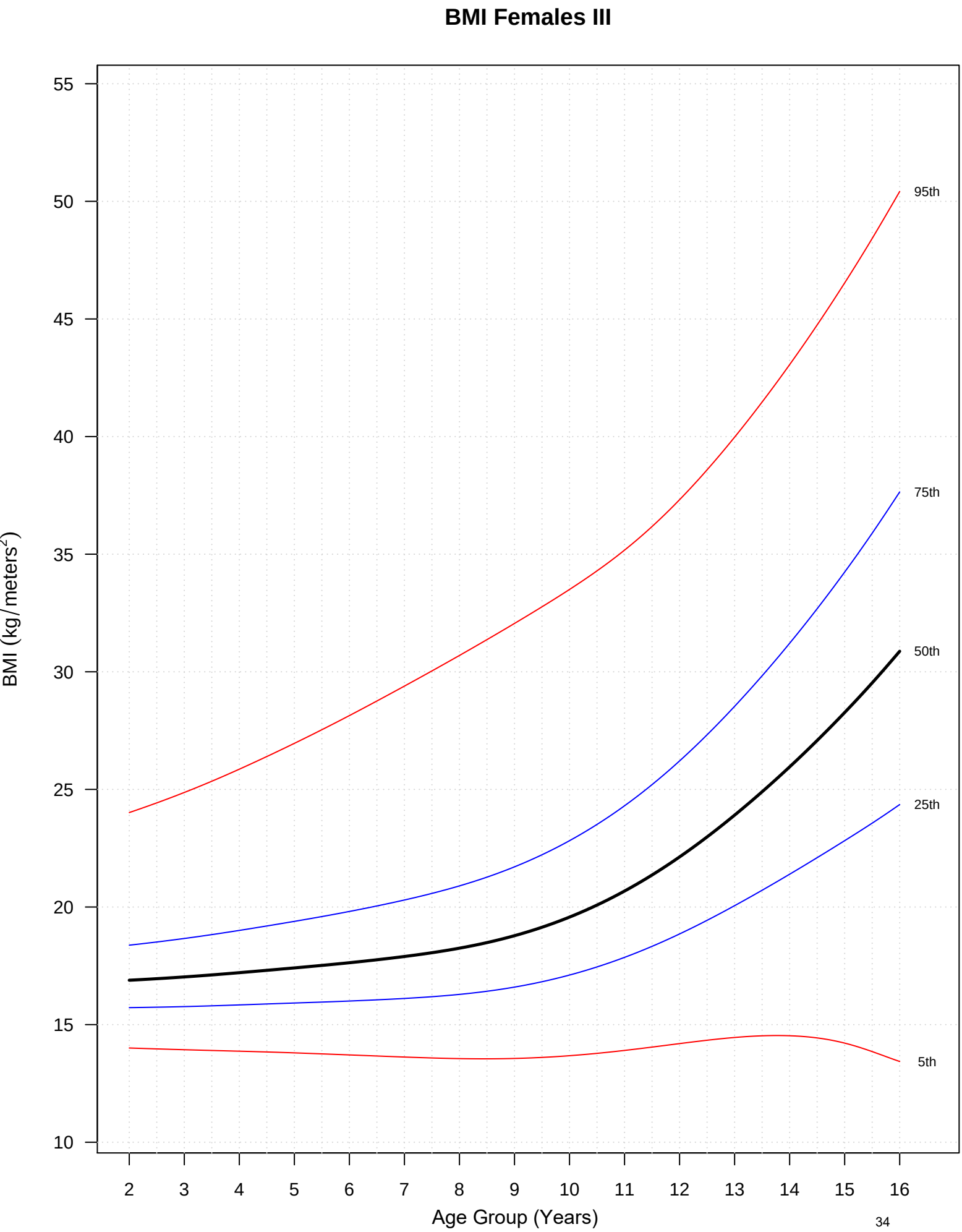

Figure S13: Longitudinal growth curves for BMI of females with type III OI.

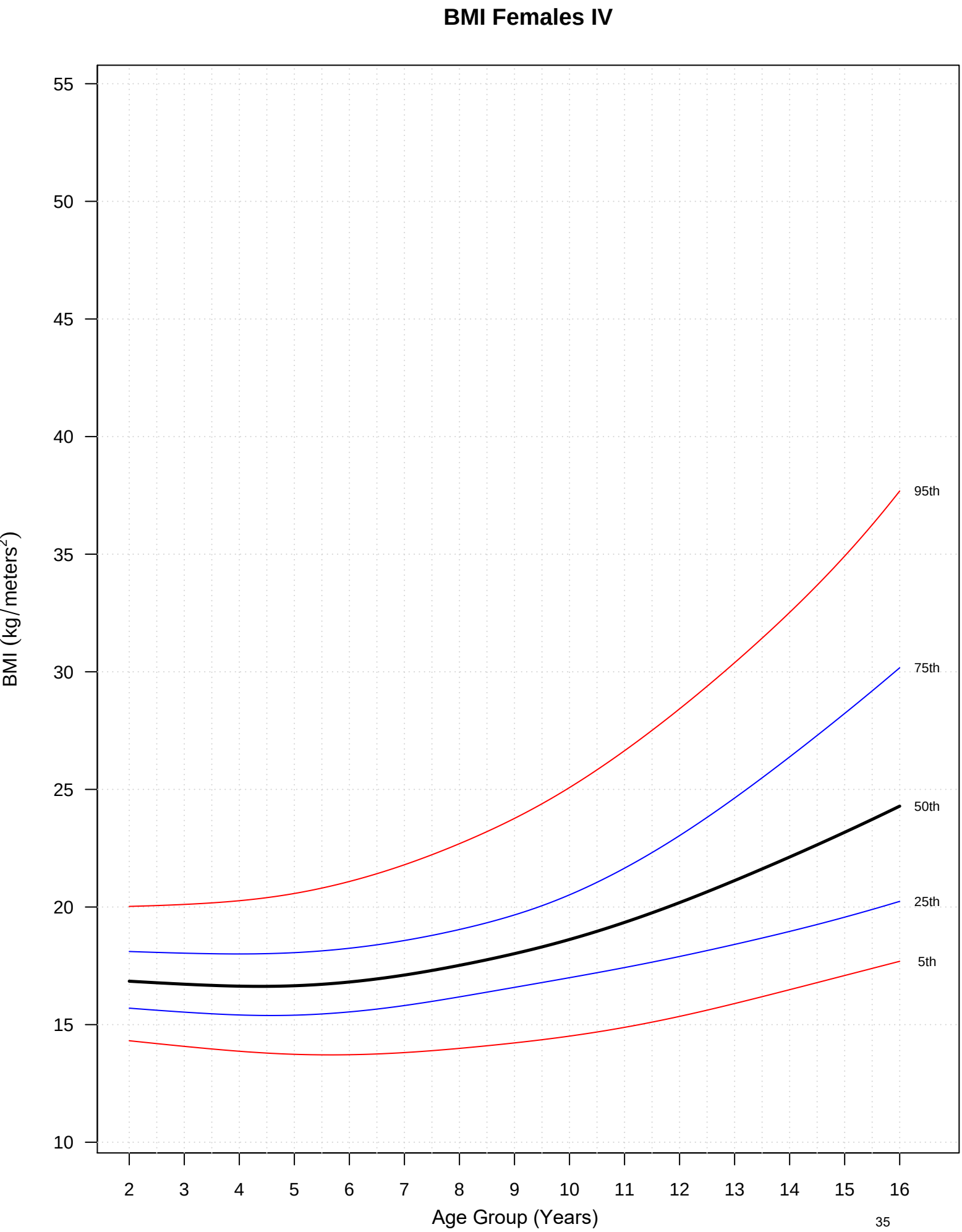

Figure S14: Longitudinal growth curves for BMI of females with type IV OI.

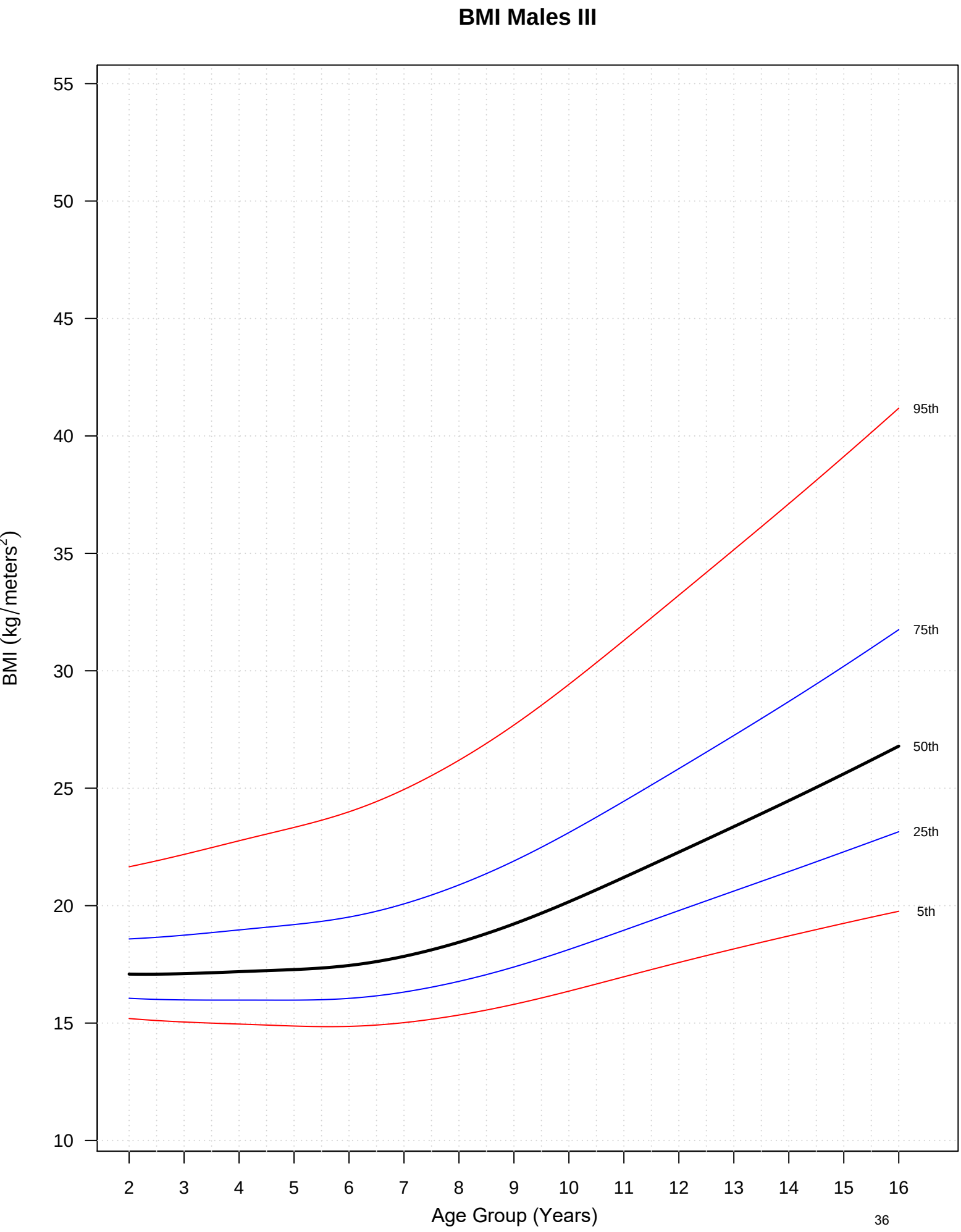

Figure S15: Longitudinal growth curves for BMI of males with type III OI.

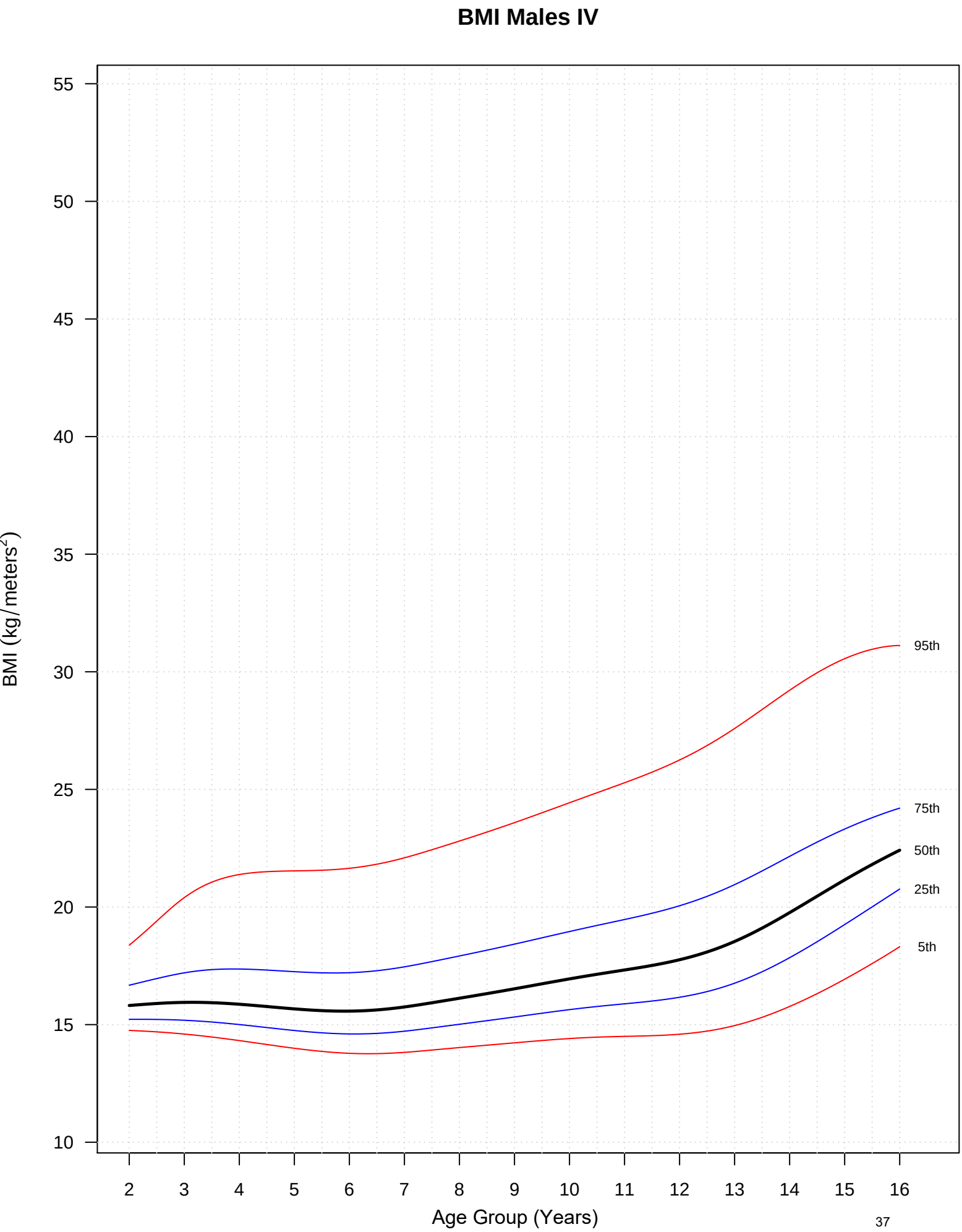

Figure S16: Longitudinal growth curves for BMI of males with type IV OI.