Demystifying LMS and BCPE Methods of Centile Estimation for Growth and Other Health Parameters

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Lambda-Mu-Sigma and Box-Cox Power Exponential are popular methods for constructing centile curves but are difficult to understand for medical professionals. As a result, the methods are used by experts only. Non-experts use software as a blackbox that can lead to wrong curves. This article explains these methods in a simple non-mathematical language so that medical professionals can use them correctly and confidently.

Keywords: *Anthropometry, Gaussian distribution, Percentiles.*

Centile curves, such as for weight and height of children, plot various percentiles at different ages. When constructed for healthy children, these are used as reference for evaluating growth of children. Main feature of these plots is that percentiles look like a smooth curve over age. Two major statistical problems involve into making these curves. First is to find different percentiles at each age and second is to achieve smoothness of the percentile curves over age.

Lambda-Mu-Sigma (LMS) [1] and Box-Cox Power Exponential (BCPE) [2] are popular methods to obtain smoothened centile curves, particularly for cross-sectional data. These are commonly used to obtain percentile curves for various growth parameters in children such as by World Health Organization (WHO) Multicentre Growth Reference Study (MGRS) Group [3] and growth reference curves for school-aged children and adolescents [4]. The application extends to any setup where centiles are estimated for different time points. For example, these methods have been used to obtain reference values of differences between TW3-C RUS and TW3-C carpal bone ages of children in China [5], to obtain centile charts for placental weight for singleton deliveries in Aberdeen, UK [6] and for normal values of aortic dimensions, distensibility, and pulse wave velocity in children and young adults in Germany [7].

Despite such diverse use, the methods seem to have never been explained explicitly. Mathematical details have been provided [2,4] but they seem to be too complex for medical and health professionals. It is not immediately clear from these explanations why such complicated methods are required, which part of the methods is for centile estimation and which part is for smoothening, and among smoothening, what is for estimates of parameters and what for centile curves: WHO report [8] has explained the essentials but not the details. Because of several unexplained steps, the application so far has not been widespread. It been done either by experts who know the intricacies or by inexperts who use the software as a blackbox [9].

The purpose of this article is to demystify LMS and BCPE methods alongwith the methods of smoothing so that health professionals can use them correctly with a degree of confidence. However, some finer details such as intricacies of percentiles beyond 99th and below 1st, and details of the competing methods have been left out from the present article so that the article remains short and intelligible for health professionals. This article also does not discuss aspects of data collection (age intervals, longitudinal/cross-sectional), data cleaning and outliers, sample size, etc. Only the most commonly applicable statistical methods for cross-sectional data are presented. For those interested, Borghi et al. [10] have reviewed 30 methods of constructing centile curves.

CENTILE ESTIMATION AT ONE PARTICULAR POINT IN TIME

Restrict for the time being to a specific time point, denoted by t, say age 4 years so that $t = 4$. A sample of subjects is measured for an outcome variable such as weight at that age. Since weight is the most common of such variables, most of the intricacies are explained using this as an example. Denote this outcome variable by y.

Non-Gaussian distribution

Fundamental quantity in centile estimation is the *z*-score. This is obtained as the deviation from a central value such as mean or median in standard deviation (SD) units [$z = (y$ – mean)/SD]. Interpretation of these *z*-scores is straight forward in terms of percentiles when the *y*-values follow an exact Gaussian distribution. For example, $z = 1.96$ corresponds to 97.5^{th} percentile and $z = 1.28$ to 90^{th} percentile of a Gaussian distribution. Software gives these percentiles easily for any value of *z*. The problem starts when the distribution of the response variable *y* is not Gaussian.

For a Gaussian distribution, the frequency curve should be unimodal, symmetrical (i.e., skewness = 0) and with normal peak (kurtosis = 0). Departures can be in terms of negative or positive skewness or in terms of too sharp (kurtosis < 0) or too flat peak (kurtosis > 0). Mild departures from Gaussian pattern do not matter as they may be within sampling fluctuations but it is hard to say what departures are mild. Graphical and computational methods such as Q-Q plot, box plot, and Shapiro-Wilks test have been described to check Gaussianity [9]. Tests for skewness (Sk) and for kurtosis (Kurt) are also applied for centile estimation. For skewness, generally |Sk| > 0.5 is considered high. Else, calculate $z = |Sk|/[SE(Sk)]$ and reject the null of Sk = 0 if this $z > 2$: $SE(Sk) = \sqrt{(6/n)}$ for large *n*. Similarly, |Kurt| > 1.0 is considered high, else reject null of Kurt = 0 if $z = |Kurt|/SE(kurt) > 2$; $SE(Kurt) = \sqrt{(24/n)}$ for large *n*.

Fig.* 1** shows the distribution of weight of 272 children (assume girls for our purpose) of age 48 months (±3 months) in Nepal as found in 2011 Demographic Health Survey [11]. I have changed a few values to illustrate the method. It looks from ***Fig.* 1** that the distribution is approximately Gaussian but that really is not so. While skewness can be "seen", kurtosis is not easy to decipher. Carefully note for our data that weights between 12.0 kg and 14.0 kg are more common than expected under Gaussian distribution (Fig. 1***), indicating a flatter peak. Also the weights in right half of the plot have slower decline and this tail is longer compared with the left tail. This indicates positive skewness. This is the kind of pattern generally followed by weight in children. The descriptive statistics for this dataset (***Table* I**) show that the distribution is positively skewed with Sk = +0.654; statistical software calculated this easily. This Sk is > 0.5. Otherwise too, $z = Sk/[SE(Sk)] = 0.654/0.148$, which is >2 and you can reject the null of Sk = 0. Similarly, Kurt = 1.043, which also is statistically significant since SE(Kurt) = 0.294 for these values (***Table I***). This all suggests that the distribution is not Gaussian.

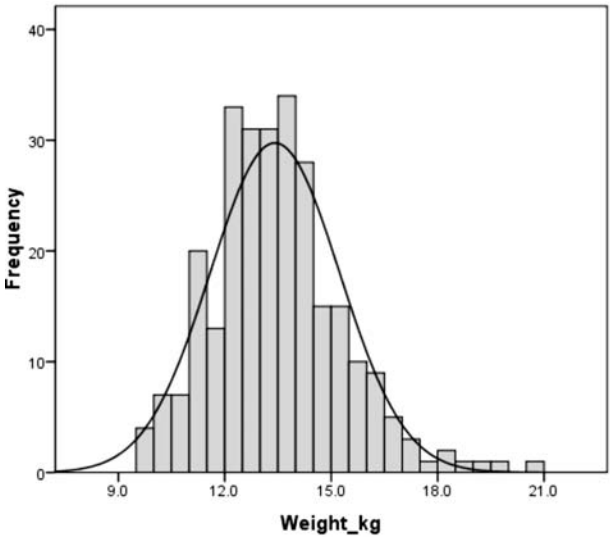

FIG. 1 *Weight distribution of 4-year old girls with corresponding Gaussian distribution superimposed.*

When the distribution is skewed and kurtotic, *z*-scores do not have a valid interpretation. Thus we need to transform the distribution to (Gaussian or approximately so) before *z*-scores can be correctly used. Here in comes the role of LMS and BCPE methods.

LMS Method

LMS method is primarily for correcting skewness. It does not handle kurtosis. BCPE method, described later, handles both skewness and kurtosis. Thus use LMS method to find *z*-scores when the distribution is skewed but have 'normal' peakedness and use BCPE method when *z*-scores are to be corrected for non-normal peakedness also.

TABLE I DESCRIPTIVE STATISTICS FOR THE DATASET OF WEIGHT (KG) OF 4-YEAR-OLD GIRLS ($N = 272$)

Parameter	*Value*
Mean	13.41
Median	13.35
Mode	13.60
Standard deviation	1.82
Variance	3.324
Skewness	0.654
Standard error of skewness	0.148
Kurtosis	1.043
Standard error of kurtosis	0.294
Range	10.9
Minimum	9.6
Maximum	20.5

Square-root transformation tends to correct mild positive skewness. This transformation shrinks the y-values but important is that higher values shrink more than lower values. In terms of power of y square-root is $y^{0.5}$. When applied to the distribution in ***Fig.* 1**, the net effect will be that right skewness will considerably reduce, may even vanish. On the other hand, if the distribution is negatively skewed with longer left tail, the transformation $y^{2.0}$ will do just the reverse. It will stretch right tail much more than left tail – thereby tends to correct left skewness. Both these transformations are of the type y^{λ}. This is called power transformation and is a potent tool to correct skewness. The value of power λ depends on the type of skewness and the extent of skewness. In our data, skewness is 0.654 (***Table* I**) and λ is to be chosen accordingly as per the procedure explained later in this article.

Now introduce another transformation. Divide each y by its central value μ and calculate y/μ. This central value could be mean or median or any other value. Since mean is not a good representative central value in case of skewed distribution, other options remain for exploration. For example, in our weight data of 4-year olds, mode is 13.6 kg (***Table* I**). If we divide each weight by this, values less than 13.6 will become less than 1.0 and values more than 13.6 would become more than 1.0. Now the transformation makes more sense. Now the square-root transformation is $(y/\mu)^{0.5}$ and square transformation is $(y/\mu)^2$. In general, the power transformation is $(y/\mu)^{\lambda}$. $\lambda > 1$ is for correcting left skewness and $\lambda < 1$ for right skewness. If the distribution is already Gaussian, no correction is required, and then $\lambda = 1$.

LMS method [12] uses the following transformation, which is an extended form of power transformation discussed in the preceding paragraph:

$$\text{(A)}\quad z_{\text{LMS}} = \frac{1}{\sigma_L \lambda}\left[\left(\frac{y}{\mu}\right)^{\lambda} - 1\right] \text{ for } y, \mu, \sigma_L \text{ and } \lambda \neq 0,$$

where σ_L is a measure of dispersion as shortly explained. This transformation is called reparametrization. The original measurements such as weight in our example may have any skewed distribution with single mode, the distribution of z_{LMS} with this transformation will be standard normal and this will give the correct z-score for calculating the percentile provided the kurtosis is already zero. Note the involvement of lambda (λ), mu (μ), and sigma (σ_L), making it a LMS method. The rationale of $(y/\mu)^{\lambda}$ is already explained and σ_L is in the denominator just as is σ in $z = (y - \mu)/\sigma$. But in LMS, σ_L is the coefficient of variation σ/μ. Note that when $\sigma_L = \sigma/\mu$, and $\lambda = 1$, equation (A) reduces the usual z-score $(y - \mu)/\sigma$.

For $\lambda = 0$, z_{LMS} in equation (A) becomes indeterminate 0/0 and is replaced by its mathematically equivalent $[(1/\sigma_L)*\ln(y/\mu)]$. In this case, this becomes log transformation. Negative values of y or μ can make y/μ negative whose root (such as square-root) does not exist. All medical parameters of the type we are discussing have positive values. For example, weight can never be negative. For something like change from pre- to post-treatment or difference between, say, right and left measurements, which could be negative, this transformation would work only after adding slightly more than the minimum difference. If minimum difference is –3, add 3.1 to all the differences, and then use this method.

Now comes the first difficult part. How to estimate the values of λ, μ, σ_L? Explicit forms for estimating these parameters do not exist. Special software is used to find those values of these parameters that maximize the likelihood of the transformed values of the sample to have come from a standard Gaussian distribution with mean = 0, SD = 1, and skewness = 0. This is called the method of maximum likelihood. For example, for our data depicted in **Fig. 1**, software will find those values of λ, μ, σ_L that make the distribution of z_{LMS} closest to standard normal.

If we assume for our weight data that such estimates are $\mu = 13.6$, $\sigma = 2.0$ (so that $\sigma_L = 2.0/13.6 = 0.147$), and $\lambda = 0.30$, z_{LMS} for a child with weight $y = 15.0$ kg is

$$z_{\text{LMS}} = \frac{1}{0.147 \times 0.30}\left[\left(\frac{15.0}{13.6}\right)^{0.30} - 1\right] = 0.0298/0.0441 = 0.6757,$$

and the corresponding percentile from Gaussian table is 75. Thus this child's weight is better than 75% children in this population. Instead of LMS, usual z-score, which is uncorrected for skewness, is $(15.0 - 13.41)/1.82 = 0.874$, where mean and SD are from Table 1. This value of z corresponds to 81st percentile. Note how z-scores with no correction and LMS correction give very different values of percentile for the same child. This is because of skewness in the data.

There is a mathematical relationship between usual z and LMS percentile:

$$\text{(B)}\quad p^{\text{th}} \text{ percentile} = \mu(1 + \lambda\sigma_L z_p)^{1/\lambda},$$

where z_p is the usual value from Gaussian table corresponding to p^{th} percentile. For example, for 75th percentile, $z_p = 0.675$ from Gaussian table. Thus, 75th LMS percentile = $13.6 \times (1 + 0.30 \times 0.147 \times 0.675)^{1/0.30} = 13.6 \times 1.103 = 15.0$. We have just shown that weight = 15.0 kg is at 75th percentile. Inverse calculation also reveals the same. Once estimates of l, μ, s_L are obtained, equation (B)

shows that it is very easy to calculate percentiles at any particular age for a skewed distribution. LMSchartmaker (Medical Research Council, UK) is the software of choice for this purpose.

BCPE method

Now consider a distribution of y that has positive or negative kurtosis. Weight distribution of 272 girls in ***Fig.* 1** has kurtosis = 1.043. This was shown earlier to be statistically significant. Because of high kurtosis, z_{LMS} will undesirably give high or low z-score. Thus it is necessary to model kurtosis as well. For this, additional adjustment is needed. This adjustment is not in terms of a new transformation but is in terms of considering that distribution of z_{LMS} is not standard Gaussian but another complex looking distribution called BCPE distribution (BCPE). This is where BCPE comes in. Beside λ, μ, σ, this distribution has another parameter denoted by τ. However, now skewness parameter λ is denoted by ν as λ would be the notation for power transformation of t-variable. Note that λ earlier used for age transformation is different from λ now being used for measurement transformation. BCPE distribution reduces to LMS when $\tau = 2$. Thus LMS method is a special case of BCPE method. One might just as well straight try to use BCPE method. This will give $\tau \approx 2$ if the kurtosis is already zero. Again, the values of μ, σ, ν and τ are estimated with the help of special software. This is also called LMSP method.

p^{th} percentile for BCPE distribution is obtained by using an inverse function but it does not have an explicit expression of the type we have in equation (B) for LMS method. Software help will be required. The details are given elsewhere [2].

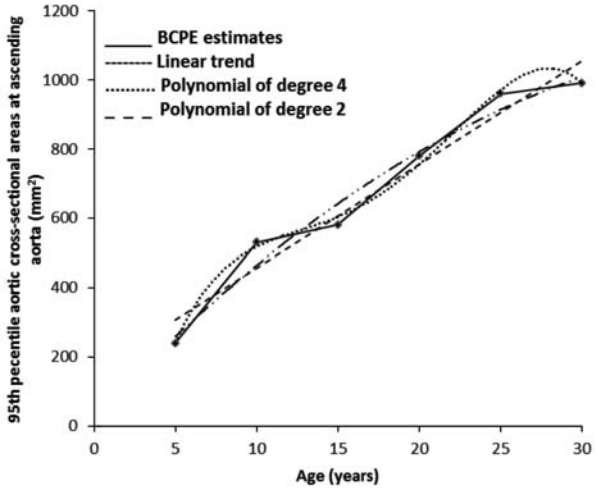

FIG. 2 *Trend of 95th percentile of aortic cross-sectional areas at ascending aorta at different ages*

CENTILE CURVE OVER A PERIOD OF TIME

The discussion so far is for centile estimation at one particular value of t-variable such as age = 4 years. For centile curves, this estimation is done for many points in time. For example, for weight curve, one would obtain, say, 97.5th percentile for age 1 year, age 2 years, age 3 years, etc., to able to obtain centile curve. It is fair to expect that these percentiles at different ages would follow some kind of smooth trend. But, unfortunately, that would not be so, mostly due to sampling fluctuations. Real statistical problem starts from here. These percentiles would, in all probability follow an irregular pattern as are BCPE based hypothetical estimates in ***Fig.* 2**. These are 95th percentile of aortic cross-sectional areas at ascending aorta at different ages, similar to those obtained by Voges, *et al*. [7]. It would be unrealistic that one age gives a high area and the next a relatively a low area unless there is a biological explanation. Extracting a realistic trend from erratic values is a great statistical challenge.

Eyeball trend can be fitted but that lacks scientific basis and could vary from person to person. Shown in the ***Fig.2*** are observed values by solid line, linear trend by dashed line, polynomial of degree 4 by dotted and polynomial of degree 2 by spaced dashes. The difficulty is to ascertain that flattening at 15 years in ***Fig.* 2** is real (does the aorta area really increases slowly between age 10 and 15 years?) or that is just because of sampling fluctuation – another sample may not give this trend. If this flattening is genuine and we ignore this in our trend, important information regarding a slow down just before age 15 years is lost. For delineating norms, no genuine information can be sacrificed. Also, a similar slow-down is noted after age 25 years. None of the four trends in ***Fig.* 2** seems adequate to provide a real picture. Biological knowledge suggests that the aorta area increases rapidly till age 20 or 25 years and then the increase slows down, particularly in those who have relatively large area for their age (say, those on 95th percentile). Thus a flattening between 25 and 30 years seems real but not between age 10 and 15 years. This is resolved by smoothing.

However the first step is resolving an entirely different problem that relates to the t-variable such as age. Smoothing of centile curves will be taken up in steps 2 and 3.

Step 1. Age transformation

Almost all growth parameters (height, weight, chest circumference, etc.) increase much more rapidly in first few months of life compared with the later ages (***Fig.* 3**, left panel). Whatever smoothing is done, if it works well

for early age, it tends to distort trend in later ages, and if it works well for later ages, it may distort trend in early age. To overcome this problem, age (or whatever is *t*-variable) is transformed before exercise on smoothing of centile curve is undertaken. Steeper curve at the beginning of life suggests that a transformation of the type t^{λ} will have an assuaging effect. In right panel of ***Fig.* 3** is the same curve but age is now scaled to age$^{0.6}$ so that $\lambda = 0.6$ in this case. Convention is to try all values of λ between –1 and 2 at an interval 0.25 (i.e., –1, –0.75, …, 0, 0.25, 0.50, …, 1.75, 2.00), and choose that value which transforms the relationship to nearly linear. When relevant software is available, this is not a difficult exercise. Call this λ_0. This would be the initial value and refined later as shortly explained.

Step 2. Smoothing of L, M, S, and P curves

Trend finding inherently ignores some dips and bumps. We wish to consider these because they could be real. Thus, in this case, we use the term smoothing in place of trend. Smoothing tries to retain the short-term increasing and decreasing trends (ups and downs) as they could be real biological features.

Direct smoothing of centile curves can be done but this may not work well because smoothing each centile curve separately may not synchronize with each other. For example, 50th percentile curve may show faster rise and 95th could be rather flat, and this could give inconsistent results. Thus a longer but more appropriate route is adopted. This involves smoothing the estimates of LMSP (μ, σ, ν, τ) parameters. Along with λ for time points, the model is called BCPE(μ, σ, ν, τ, λ). Note that first four parameters in this pertain to the variable *y* such as weight whereas the fifth pertains to *t*-variable such as age.

Best estimate of each of μ, σ, ν, and τ for each time point are obtained from the procedure outlined in the previous section. These estimates can be plotted versus time. Thus there is one μ-plot, one σ-plot, one ν-plot and one τ-plot. Sometimes they are referred to as L-plot, M-plot, S-plot and P-plot, although not in this sequence. As in the case of percentiles, these plots will be irregular (see ***Fig.* 4** for ν-plot for 1-month weight velocity). For smoothing these plots as curves, Cole and Green [2] suggested a method of penalized likelihood estimation, which incidentally leads to natural cubic splines with knots (also called control points) at each distinct value of *t*. In fact both penalized likelihood and cubic splines are equivalent methods.

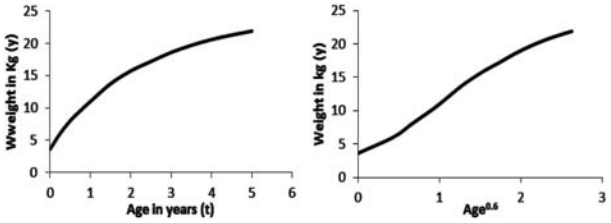

FIG. 3 *Effect of age transformation on centile curve.*

For implementing the method just mentioned, most researchers now use software called Generalized Additive Model for Location, Scale and Shape (GAMLSS) [13]. The procedure requires estimating parameters of smoothness, also called effective degrees of freedom (edf). For example, edf = 1 means just a point, edf = 2 means that the curve is smoothed as a straight line, edf = 3 means that the curve is smoothed almost as a quadratic curve and edf = 4 means that the curve is smoothed as nearly a cubic polynomial. These edfs will be used to get the estimates of the parameters μ, σ, ν, τ at different ages. Each curve will have its own edf depending on how many identifiable twists and turns that curve has over age. These may also differ from boys to girls in case of growth indicators. These edfs are also referred to as smoothing parameters and are derived from penalized maximum likelihood function as stated earlier, using GAMLSS software.

Since higher edfs give increasingly complex curve, smoothing will not be so smooth if the higher edfs are used. The objective is to find least edf that will still provide a good fit to the observed trend of L, M, S, and P values over time points. Balancing the smoothness and goodness of fit is ultimately the researcher's call but one can take help of a goodness of fit index such as Generalized Akaike Information Criterion (GAIC). In this case, this takes the

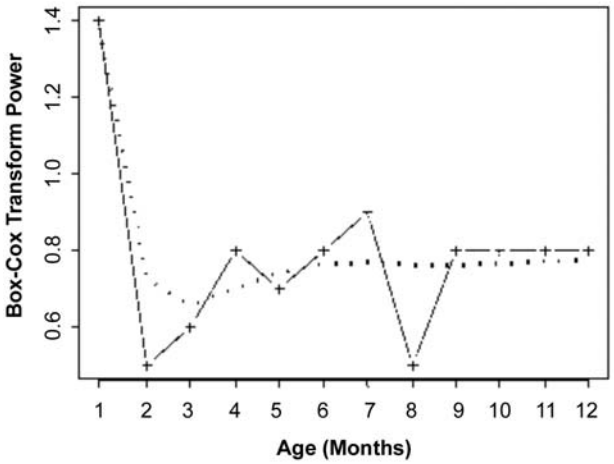

FIG. 4 *Fitting of n-curve for selected model for 1-month weight velocity for boys (Dotted is the fitted curve and solid lines are the estimated values of n at different ages) (Source: WHO report [8], page 36)*

form GAIC(3) = $-2L + 3p$ where L is the log-likelihood and p is the total of all edf*s* + 1 for estimating parameter λ. This 3p represents the penalty on the likelihood for achieving greater smoothness. Smaller is the value of this criterion, better is the fit. Experience suggests that this penalty of 3p works better (in the sense of providing smoother curves) than any other penalty for estimating these edfs. If you find $\nu = 1$ and/or $\tau = 2$, you can keep them fixed.

GAMLSS uses iteration method and needs to start from some assumed values of μ, σ, τ, ν, and λ. Note that it includes λ whose initial value is λ_0 as obtained earlier. An automatic procedure is available in GAMLSS that uses these starting values and provides optimal values of edf(μ), edf(σ), edf(ν), and edf(τ), which minimize GAIC(3) [2]. Start can be with any appropriate looking values but it is advisable to try out low, medium and high starting values (except for λ since the initial value of this is λ_0) to achieve global minimum of GAIC(3) [2]. Alternatively, option is available in the software that would choose the starting values also for you.

For example, the specifications of the BCPE models that provided the best fit to generate the growth curves of school children and adolescents in the US were as follows [4]. For height-for-age: BCPE($\lambda = 1$, df(μ) = 12, df(σ) = 4, ν = 1, τ = 2) for boys; and BCPE($\lambda = 0.85$, df(μ) = 10, df(σ) = 4, ν = 1, τ = 2) for girls. For weight-for-age: BCPE($\lambda = 1.4$, df(μ) = 10, df(σ) = 8, df(ν) = 5, τ = 2) for boys; and BCPE($\lambda = 1.3$, df(μ) = 10, df(σ) = 3, df(τ) = 3, τ = 2) for girls. As stated earlier, df(μ) is the effective degrees of freedom (although prefix e is dropped in these expressions) for the cubic splines fitting the median (μ); df(σ) the degrees of freedom for the cubic splines fitting the coefficient of variation (σ); df(μ) the degrees of freedom for the cubic splines fitting the Box-Cox transformation power (ν) (for height-for-age fixed $\nu = 1$); and τ is the parameter related to the kurtosis (in both the cases fixed $\tau = 2$) [4].

There is a word of caution, though. Cubic splines use the values at both the sides of knots—if t is the knot, values before t and values after t are used. Thus the method of penalized likelihood estimation, since based on cubic splines, is weak at the two ends of the series as only half the information is available—only the past for highest end-point and only the future for the lowest end-point. For example, if the highest age under observation is 14 years, the estimates of various edfs will work well for upto the age of 13 years.

Step 3. Testing the goodness of fit of the final curves

Step 2 will provide 'best' estimate of edfs. Use these to plot LMSP curves versus age and find the values of estimated μ, σ, ν, τ, and λ at each age of interest – estimate of μ at each age from μ-curve, estimate of σ at each age from σ-curve, etc. Use these age-specific estimates to find different percentiles at each age using BCPE distribution.

Final step is to check the fitting of the centile values with the observed data since curves so arrived may still be far from the observed values. For this, Q-test [14] is used. This combines overall and local tests assessing departures from the normal distribution with respect to median, variance, skewness and kurtosis. This involves calculating z-scores at each age and then for all ages combined separately for each parameter (μ, σ, ν, τ, and λ). Absolute z-value larger than 2 at any age indicates lack of fit. Other goodness of fit tests for age-related reference ranges and their comparison are reported elsewhere [15].

Interpretation of Q-test results requires considering shape of worm plots [16] but let us not go into that complexity. In case of lack of fit, recalibrate values of μ, σ, ν, τ, and λ. This is called fine tuning. This involves going back to the GAMLSS software and use the latest available estimates of μ, σ, ν, τ, and λ as inputs and find new estimates. Many times no improvement will occur.

It should be clear from this description that both LMS method and BCPE method are calculation intensive and can not be used without the help of appropriate software.

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