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Abstract

Reference charts are valuable tools for clinicians in their daily work on pediatric clinics. Reference charts are often constructed by smoothing techniques, and in this paper we present a newly dev

1 Introduction

reference chart is a graph showing the distribution of some measurement of interest and age. This is usuall done b displa ing the median and various percentiles over the range of ages. When the measurements are approximatel normall distributed, perhaps after an appropriate transformation, the median is equivalent to the mean and this is usuall used for estimation purposes. Further, when measurements are approximatel normal the percentiles can all be expressed as a simple function of the mean and the standard deviation. Therefore it often suffices to estimate a mean function that relates the expected value of the measurement to age, and the variance function that relates the variation of measurements to age. The mean curve and the variance function ma be estimated when some assumptions are made, usuall one assumes that the are smooth curves, and then uses a smoothing technique to estimate the curves. Quite often smoothness is a reasonable assumption that can be justified based on biological reasoning. Even with smoothness, however, man difficulties are still present, and these are not the issue of this paper. Cole Green[1] reviews methodological issues of construction for reference charts.

It is important to distinguish between reference charts used for cross-sectional purposes, i.e., deciding whether or not a given measurement at a given age is normal compared to the distribution in a comparable population, or longitudinal purposes, i.e., deciding whether or not the growth of a child is normal based on repeated measurements. When evaluating the development of the measurement of interest the techniques used should reflect the longitudinal aspect. The t pical clinical situation is the following: a child returns for measurements at the pediatric clinic, or shows up with a record of earlier measurements, now, based on the current and the

2 A Lo -Rank Test for Co parin Re ression Functions

In this section we present a longitudinal regression model, for independent identicall distributed subjects, that models the current measurement given the time it was measured, the previous measurements and the times of these, see Scheike[4] or Scheike Zhang[3] for further details. This is expressed through the conditional regression model

$$Y_{i,j} = m(V^i_{\tau_{i,j}}) + \epsilon_{i,j}, \qquad \text{for } j = 1, ..., N_i, \ i = 1, ..., n. \tag{1}$$

Think of $Y_{i,j}$ as the j^{th} measurement of the i^{th} subject at time $\tau_{i,j}$. We assume that $m(\cdot)$ is a smooth function and that V^i_s is an observable process that onl depends on past observations. Note that the regression

where is introduced to avoid edge effects of the kernel estimators. Using local-linear smoothers, or smoothers without edge-problems, this issue can be ignored for applications.

Scheike Zhang[3] studied the as mptotic distribution of $T(z)$ and showed that if $n_j/(n_1+n_2) \to p_j$, for $j = 1, 2$, and under sufficient smoothness and other weak regularit conditions, it follows that $\sqrt{n_1+n_2}T(z)$ converge towards a Gaussian martingale with mean zero (under the h pothesis) and variance function

$$H(y) = p_1^{-1} \int_a^z \frac{\sigma_1^2(y)}{\alpha_1(y)} + p_2^{-1} \int_a^z \frac{\sigma_2^2(y)}{\alpha_2(y)},$$

that can be estimated consistentl b

$$\widehat{H(y)} = (\frac{n_1}{n_1+n_2})^{-1} \int_a^z \frac{\widehat{\sigma_1^2(y)}}{\widehat{\alpha_1(y)}} dy + (\frac{n_2}{n_1+n_2})^{-1} \int_a^z \frac{\widehat{\sigma_2^2(y)}}{\widehat{\alpha_2(y)}} dy$$

One consequence of the Proposition is that

$$\sqrt{n_1+n_2}T(z) \approx N(0, H(y)),$$

i.e., $T(z)$ is approximatel normall distributed with a variance we can estimate.

We now define the log-rank (two-sample) test-statistic of the h pothesis $H_o : m_1(\cdot) = m_2(\cdot)$ on the interval $[\ , S - \ ]$ as

$$LR = \sqrt{n_1+n_2}T(S - \ )/\sqrt{\widehat{H}(S - \ )}$$

where S is the upper limit of comparison. The two sample log-rank test, LR, have an as mptoticall standard normal distribution under the the null h pothesis of $m_1(z) = m_2(z)$ on $[\ , S - \ ]$. The test-statistic works best if $m_1(\cdot) \leq m_2(\cdot)$ or $m_2(\cdot) \leq m_1(\cdot)$.

If this is not the case one ma instead consider the maximal deviation test-statistic

$$M \stackrel{\text{de}}{=} \sup_{z \in [a, S-a]} |T(z)|. \tag{4}$$

To work out the log-rank test-statistic we thus need to have estimates of $m_k(\cdot)$, $\sigma_k^2(\cdot)$ and $\alpha_k(\cdot)$, and we therefore propose that these are given when reference charts are presented. The next two section consider the implementation of the log-rank test-statistic in two practical situations. Section 3 contains and application to cross-sectional data, and Section 4 discusses a longitudinal situation.

3 Co parin Cross-Sectional rowth Data

The average height in the population has been increasing with time - the so called "secular trend". Consequentl , construction of reference charts for height must be renewed regularl . The secular change in mean height in a population is the result of a general

and an estimate of the variance of this quantit

$$\widehat{H} \quad = \quad \sum_i (\ _{1,i+1} - \ _{1,i}) \frac{s_{1,i}}{f_{1,i}} + \sum_i (\ _{2,i+1} - \ _{2,i}) \frac{s_{2,i}}{f_{2,i}}.$$

Then the the log-rank test-statistic is computed as $LR = T/\sqrt{\widehat{H}}$. Using the summations provided in the table we get $T = 1985.0 - 1952.2 = 32.8$ and $\widehat{H} = 9.2 + 0.8 = 10.0$ which results in a log-rank test-statistic of LR=10.3, that is approximatel standard normal under the null-h pothesis, and therefore is equivalent to a p-value less than 0.0001.

The average height of the recent stud is 3.5 cm greater than the Danish standard from ndersen et al.[5]. This equals approximatel 0.5 standard deviation (depending on age) and implies that, with the use of the reference charts based on heights obtained more that 20 ears ago, a smaller fraction of short children in 1992 will be classified as pathologicall short, i.e., with a height that is more that 2 standard deviations smaller than the average height. The difference between the 2 studies must be ascribed to socio-economic differences and secular changes.

4 Co parin Lon itudinal rowth Data

In this section we wish to compare the growth of patients with two t pes of skeletal d splasia, namel h pochondroplasia (H po) and achondroplasia (cho). Our data were provided b the Department of Growth and Reproduction at the Universit hospital in Copenhagen and consists of longitudinal measurements of height and weight for 36 patients with h pochondroplasia and 42 patients with achondroplasia.

Skeletal d splasias represent more than 200 different clinical t pes of short limbed dwarfism of which chondroplasia and H pochondroplasia are the most common t pes of skeletal d splasias. The sewere dwarfism and d sproportion of the bod in patients with achondroplasia is caused b a point mutation on chromosome 4 in the fibroblast growth factor receptor (FGFR3) gene which can be demonstrated in all patients with achondroplasia. B contrast, patients with h pochondroplasia represent a more heterogenous group; some patients have the same clinical appearance as patients with achondroplasia and similar degree of growth retardation, whereas others have an almost normal clinical phenot pe and growth. The mean standing height was approximatel 3 SD's below the mean for age-matched helath children. Point mutations in the FGFR3 gene have been demonstrated in 50-60 % of patients with h pochondroplasia onl . Whereas, several studies have reported on actual heights in patients with skeletal d splasia, little is known on possible differences in the linear growth pattern in different t pes of skeletal d splasias. We refer to Hertel[6] for further details on skeletal d splasia.

The focus of this section is on the longitudinal aspect of the data, with the specific aim of deciding whether or not the two t pes of skeletal d splasia results ina3lasia resultfl(in)30TDfl[(p)-30 2p;er

models

It appears that patients with h pochondroplasia grow faster than patients with achondroplasia, and if we appl our regression log-rank test to the the 2-dimensional regression model with the following region of previous height and time since previous measurement : $[50, 120]$ $[0.2, 1.9]$ our test statistic can be calculated for a choice of the two dimensional band-widths. Figure 2 shows the difference in the cumulative regression functions ($T(z)$) for $b_1 = 5.0$ and $b_2 = 0.2$. For this choice of bandwidths we get a test-statistic evaluated in the endpoint ($T(120, 1.9)$) on 94.1 with variance 586, and this results in a $LR = 3.9$ test-statistic which is approximatel standard normal thus resulting in a p-value of approximatel 0.0001. Further smoothing of the regression functions results in the same conclusion although the test-statistic decreases some. Note that one would expect the test-statistic to have good power in this application since the H po diagnosis appears to result in a consistentl better growth than the cho diagnosis. similar comparison of the increase

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and the methodolog is therefore limited to low dimensions. In an example we compared the longitudinal growth for two different diagnosis of skeletal d splasia where an ideal 3-dimensional regression function was reduced to a 2-dimensional regression function that provided an adequate description of the data.

6 Appendix: For ulas for esti ators

In this appendix we provide formulas for estimators of the quantities that are used in the log-rank test statistic.

We provide a Nadara a-Watson (ND) t pe estimator of the regression functions and the variance function as well as an estimator of $\alpha(y)$.

Let $(\cdot)$ be a kernel function with support on $[-1;1]$, $\int ( )d = 1$ and $\int ( )d = 0$, and let $b = (b_1, ..., b_d)$ be a d-dimensional bandwidth, $|b| = b_1 \cdot ... \cdot b_d$, $b \in]0;\infty[^d$. Define further $C_K \stackrel{\text{de}}{=} \int {}^2( )d$, $d_K \stackrel{\text{de}}{=} \int {}^2 ( )d$ and $e_K \stackrel{\text{de}}{=} \int ( )d$. We assume that e_K is 0 to obtain an as mptoticall unbiased result for our estimator. We abuse notation b letting denote a d-dimensional kernel as well as a one dimensional through the product kernel, i.e., $(y, b) \stackrel{\text{de}}{=} (\frac{y_1}{b_1}, ..., \frac{y_d}{b_d}) \stackrel{\text{de}}{=} \prod_{i=1}^{d} (\frac{y_i}{b_i})$.

Now, the ND estimator$_{y_{NW}}$Tffl10140.9998Dfl( )T1rT1108.9/T1 Dfl(()Tjfl/T111Tffl30(ND)-31000(estiT1108.9/T1

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Figure 1. Estimated mean (thin line) and data points from Copenhagen bo s 1988-1992 (dots), and estimated mean and 95 % reference area for Danish standard reference from 19 1 (thick lines).

Table 1. Estimate of densit multiplied b sample size, estimate of mean, estimate of variance, and log-rank test for difference between mean curves of Copenhagen bo s and Danish standard reference.

Figure 2. Normalised difference in cumulative regression functions for H po- cho for bandwidth (5,0.2). The log-rank test results in p-value at 0.0001.