

PRESENTING INFORMATION ON GROWTH DISTANCE AND CONDITIONAL VELOCITY IN ONE CHART: PRACTICAL ISSUES OF CHART DESIGN

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SUMMARY

Growth charts, which conventionally record only cross-sectional (distance) information, can be extended to monitor growth rate over time (velocity). To adjust for regression to the mean the velocity should be conditional on the previous measurement. By working on the SDS scale rather than the measurement scale, the only extra information required for velocity is the correlation structure of the SDS at different ages. The design and validation of such combined charts is an important part of their development. © 1998 John Wiley & Sons, Ltd.

INTRODUCTION

Michael Healy has been a key contributor to the research areas of reference ranges in clinical chemistry and age-related reference ranges in growth and development. He has also had a continuing interest in the assessment of growth of individuals over time. Three of his papers crystallize these interests,^{1–3} and together they highlight the problems – and some solutions – to the broad issues raised by the analysis of growth data.

One of his 1988 papers² provided, for the first time, a method for fitting growth centiles to skew reference data. It summarized each of a set of centiles as low-order polynomials, where the polynomial coefficients were constrained to be functions of the corresponding centile Normal equivalent deviates (NED). This process implicitly imposes a frequency distribution on the data at each age, and allows them to be converted to standard deviation scores (SDS).

Expressing data in SDS units greatly simplifies any subsequent analysis, for reasons some of which are well-known, and some less so. The aim is to adjust for age and sex, so that for a group of subjects the mean SDS is close to 0, with a standard deviation (SD) close to 1, independently of age and sex. For individuals, serial measurements (of weight, height etc.) plotted as SDS against age appear as fairly straight horizontal lines. These properties are well-known, and as long as 20 years ago the SDS was recommended as the best way to analyse and present growth data.⁴

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However, the absence at that time of a satisfactory method for expressing weight, with its skew distribution, as an SDS, delayed the subsequent development of the methodology. The method used by Waterlow⁴ for the conversion was to represent the weight distribution at each age as a sum of two half-normal distributions, the upper half having a larger SD than the lower,⁵ a fudge which led to centiles with discontinuous spacings on the chart.

Another paper published in 1988 described a method for fitting growth centiles to skew data, Cole's LMS method.⁶ Fundamentally different from Healy's method, it involved age-varying Box-Cox power transformations of the data, and also allowed simple conversion to SDS. Indeed the conversion was slightly easier than with Healy's method, which involved solving a low-order polynomial in the SDS. The availability of the two methods led to a resurgence of interest in the fitting of growth references,⁷ both methods were subsequently improved,^{8,9} and many applications of the methods have since been published.

The ability to generate growth references for a range of skew measurements like weight, skinfolds or body mass index ($BMI = \text{weight}/\text{height}^2$) focused attention on the chart's inability to assess growth over time. Constructed from cross-sectional data, with each subject contributing a single measurement, it provides a snapshot of the measurement's distribution over a range of ages, but contains no information about growth. This is a glorious irony considering that child growth world-wide is assessed with such charts.

The assessment process identifies at-risk individuals whose measurement centile, or whose rate of centile crossing over time, is extreme. There are two distinct screening instruments here, single centiles and centile crossing, but only the first can be quantified directly. Its false positive rate is defined by the centile used for the cut-off: -2 SDS corresponds to the 2.3th centile, so for the reference population 2.3 per cent can be expected to fall below it, a false positive rate of 2.3 per cent and a specificity of 97.7 per cent. Thus the choice of cut-off defines the likely false positive rate. The false negative rate for the instrument is not so easy to estimate, as discussed later.

Centile crossing over time is not an effective screening instrument, because the chart provides no information to quantify it. How much centile crossing is acceptable? Does it depend on age? Does it depend on the starting centile? The absence of answers to these questions arises directly from the absence of longitudinal information on the chart. To provide the information a velocity chart is needed, which gives centiles for the distribution of growth rate over time. This paper describes the development of such a chart, an extension of the conventional cross-sectional chart that monitors distance and conditional velocity simultaneously.

METHODS

Velocity on the measurement scale

Growth velocity is calculated as the difference between two measurements, divided by the time interval between them. So the variability of velocity (and hence the spacing of the centiles) depends critically on the time interval,¹⁰ and the velocity chart needs to be based on a prespecified time interval. For height an interval of 1 year is recommended to avoid seasonal effects,¹¹ while for weight in infancy an interval between 1 week and 3 months is suitable.^{3,12} The choice of interval is a trade-off between noise (that is, measurement error) on the one hand, and signal (ability to detect growth faltering) on the other. The mean μ and SD σ of velocity, as functions of age, are derived from a longitudinal study of the reference population over the chosen time

interval, and the velocity centiles are then calculated assuming normality. The 100 α th velocity centile for some measurement W is given by:

$$V_{W,100\alpha} = \mu + \sigma Z_{\alpha} \quad (1)$$

where Z_{α} is the normal equivalent deviate for tail area α .

Tanner *et al.*¹³ published the first velocity charts, and they have been widely used since. However, Healy, in 1974, pointed out a potential bias in the definition of velocity, due to regression of the mean.¹ In general the velocity depends inversely on the starting value. He proposed a conditional reference, where the second measurement is adjusted for the first using linear regression:

$$W_2 = a + b W_1 + \varepsilon. \quad (2)$$

The error ε is assumed $N(0, \sigma^2)$, and the 100 α th centile of W_2 given W_1 is

$$W_{2|1,100\alpha} = a + b W_1 + \sigma Z_{\alpha}. \quad (3)$$

Note that equation (2) can be rearranged as

$$(W_2 - W_1) = a + (b - 1) W_1 + \varepsilon$$

showing that a conditional reference for W_2 is numerically equivalent to a conditional reference for the increment $(W_2 - W_1)$, the only difference being that the regression coefficient is $(b - 1)$ rather than b .

Cameron¹⁴ applied this method to annual heights in British children, and in the process highlighted a practical problem. It required a separate chart for each age–sex group, more than 20 charts altogether. Perhaps for this reason conditional charts have been used little since. Even the simpler unconditional velocity chart is cumbersome in that it doubles the number of charts needed for each child. The ideal solution would be to combine the velocity and distance information in a single chart.

Velocity on the SDS scale

The terminology of chart usage – ‘centile crossing’ – hints at another approach. Why not define velocity as the rate of change of the centile rather than the rate of change of the measurement? Mathematically the centile itself is not suitable for this treatment, but the SDS, which has a one-to-one correspondence with the centile, is entirely suitable. For unconditional velocity, based on the reference population, the mean and variance of the change in SDS over a unit interval of time are given by

$$\begin{aligned} \text{Mean}(Z_2 - Z_1) &= \text{Mean}(Z_2) - \text{Mean}(Z_1) = 0 \\ \text{var}(Z_2 - Z_1) &= \text{var}(Z_2) + \text{var}(Z_1) - 2 \text{cov}(Z_1, Z_2) = 2(1 - r) \end{aligned} \quad (4)$$

where r is the correlation between Z_1 and Z_2 , each of which are assumed $N(0, 1)$. Equation (1) then simplifies to

$$V_{Z,100\alpha} = \sqrt{\{2(1 - r)\}} Z_{\alpha} \quad (5)$$

so SDS velocity centiles depend only on the correlation between successive measurements, at different ages. This is a considerable simplification over the more traditional velocity chart.

A further advantage of SDS velocity is that the centiles can be represented on the distance chart. Each velocity centile can be thought of as the difference between two SDSs, Z_1 and $Z_{2V1,100\alpha}$, say, measured one time unit apart (1 year or 1 month etc). So $V_{Z,100\alpha} = Z_{2V1,100\alpha} - Z_1 = \sqrt{\{2(1-r)\}} Z_\alpha$ from (5), and

$$Z_{2V1,100\alpha} = Z_1 + \sqrt{\{2(1-r)\}} Z_\alpha. \quad (6)$$

As $Z_{2V1,100\alpha}$ is a function of Z_1 , by specifying a value for Z_1 the two SDSs can be converted back to the corresponding measurements, and plotted on the chart. The slope of the line joining them then defines the 100 α th velocity centile. If Z_1 is defined at the youngest age on the chart, a recurrence relation can be set up so that the corresponding value of $Z_{2,100\alpha}$ becomes Z_1 for the next age interval, and so on.¹⁵ In this way a 'centile' curve is drawn which crosses the distance centiles, and whose slope at each age represents the 100 α th velocity centile. A series of such lines can be drawn at each age with different starting values of Z_1 , so children of different ages and sizes have a convenient line against which to compare their growth velocity.

The definitions of velocity on the measurement scale and the SDS scale are not in general the same. On the measurement scale the expected increment is the same for all children, whereas on the SDS scale the expected increment maintains the child's measurement on the same centile. Height and weight centiles diverge with age, so that on the SDS scale larger children are expected to grow faster than smaller children.

SDS velocity and measurement velocity are not only different, they both fail to adjust for regression to the mean. As before the solution is to use a conditional reference, of Z_2 adjusted for Z_1 , and again the algebra is simpler. The constant in equation (2) becomes 0 and the regression coefficient simplifies to r , the correlation between Z_1 and Z_2 .¹⁵ So equation (2) becomes $Z_2 = rZ_1$, which is a concise statement of regression to the mean. In addition the residual standard deviation (RSD) σ of Z_2 from the regression is given by $\sqrt{(1-r^2)}$. So equation (3), the conditional 100 α th centile, becomes

$$Z_{2|1,100\alpha} = rZ_1 + \sqrt{(1-r^2)}Z_\alpha. \quad (7)$$

As for unconditional velocity, 'centile' curves are drawn on the chart linking selected starting values of Z_1 and the corresponding $Z_{2|1,100\alpha}$ over the age range. However, unlike unconditional velocity, the curves with different Z_1 starting values at a particular age are no longer parallel on the SDS scale, due to regression to the mean. These lines are here called 'thrive' lines, as they can be used to identify the condition failure to thrive (FTT).

Comparison of equations (6) and (7) shows the effect of the regression to the mean adjustment. Clearly, if r is close to 1 the two expressions are essentially the same, so the adjustment is only useful when r is appreciably less than 1. Height, for example, tracks very strongly past infancy, with correlations between annual pre-pubertal heights consistently above 0.95 for research quality data.^{16,17} In this age range the average child stays close to her own height centile, with hardly any regression to the mean.

Unlike predicted unconditional velocity, which is different on the measurement scale and the SDS scale, conditional velocity adjusts for the starting measurement, and so is invariant to the scale of measurement. Equations (3) and (7) are identical when W is normally distributed, and are very similar when W is skew.

The slope of the velocity centile from (7) is $Z_2 - Z_1 = (r-1)Z_1 + \sqrt{(1-r^2)}Z_\alpha$. The variance of the centile (1) is given by $(1 + Z_\alpha^2/2)\sigma^2/n^1$, so by analogy, setting Z_1 to 0 for simplicity, the

variance of the velocity centile is $(1 + Z_x^2/2)(1 - r^2)/n$. The significance of the centile is

$$t = Z_x \sqrt{\left(\frac{n}{1 + Z_x^2/2} \right)} \quad (8)$$

which is independent of r .

Data

In infancy and puberty, and weight more than height, regression to the mean can be substantial. This is particularly so for weight in the first year, which is probably the most important age for growth assessment, with malnutrition throughout the developing world starting early in life and affecting millions of infants. Poor infant growth, often termed failure to thrive (FTT), can also be a problem in the developed world.

The recommendation is that weight should be measured monthly in infancy,¹² though this is not universally accepted.¹⁸ The Cambridge Infant Growth Study measured weight in 223 infants every 4 weeks from birth to 52 weeks, and at 18 months and 2 years. The data were converted to SDS using the revised version of the British 1990 growth reference^{19,20} and the correlation matrix between the SDS at the 16 ages calculated, with the sexes pooled. The $15 \times 16/2 = 120$ correlations were transformed to Fisher's Z and each modelled as a function of the two ages, using fractional polynomials²¹ of the mean age and age interval. The smoothed correlations were used to construct a thrive line chart based on 4-week velocity in the first year. The correlation matrix between 4 and 104 weeks was modelled previously.²²

The British 1990 growth reference has 9 distance centiles spaced two-thirds of an SDS apart.²³ Being able to add velocity centiles requires a decision as to how many and which centiles to use. In practice only one centile from each tail of the distribution is feasible, otherwise the chart gets too cluttered, and here the 5th and 95th velocity centiles are used, spaced two-thirds of an SDS apart at birth.

RESULTS

Figure 1 gives the 4, 8 and 12 week correlations for weight SDS during the first year, both observed and as predicted from a regression model for all 120 correlations in the first 2 years. The correlations are higher at older ages and over shorter time intervals. The regression coefficients for the model are given in Table I, Fisher Z transformed correlation regressed on fractional polynomials of the mean age and the age interval. The model accounts for 99.3 per cent of the variation.

Figure 2 shows the family of 5th and 95th conditional weight velocity centile curves for 4-week intervals, plotted on the SDS scale against age in the first year; the 5th centiles fall and the 95th rise. The curves change faster in the early weeks than later, and the higher curves faster than the lower, reflecting regression to the mean. Figure 3 shows the same centiles for girls plotted on the weight scale, with 9 distance centiles. They show substantial differences in velocity depending on the infant's age and weight centile. In particular, the 5th velocity centiles are negative in slope later in the first year, corresponding to weight loss rather than gain.

The chart is used in the following way. Measurements 4 weeks apart are plotted on the chart, and the line joining successive measurements is compared for slope with the nearest thrive line

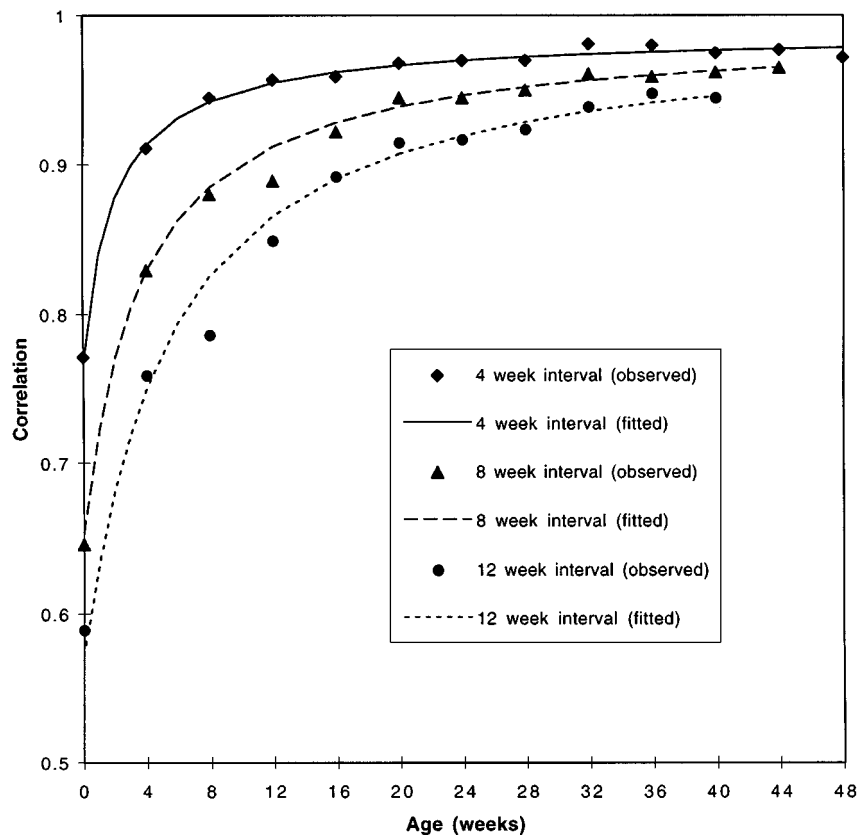


Figure 1. Comparison of observed and fitted correlations for weight SDS at different ages across 4, 8 and 12 week intervals, based on the model in Table I

Table I. Regression of Fisher's Z transform of the correlations between weight SDS at different ages, on functions of the mean age and age interval

Item	Regression coefficient	Standard error	<i>t</i> on 114 d.f.
Constant	3.1775	0.0982	32.37
$\ln(\text{mean age})$	0.3256	0.0368	8.85
$\ln(\text{age interval})$	-1.4811	0.0475	-31.17
$(\text{age interval})^{-1}$	-2.029	0.158	-12.84
$\ln(\text{mean age}) \times \ln(\text{age interval})$	0.1991	0.0116	17.18
$\ln^2(\text{mean age})$	-0.04601	0.00909	-5.06
Variance accounted for 99.3 per cent	Residual standard deviation 0.0412		

(5th centile). So long as the infant's growth rate exceeds that for the thrive line, that is, the infant's slope is greater, growth is adequate.

The chart assumes that weight measurements are made every 4 weeks, which is often unrealistic. Over time intervals shorter than 4 weeks weight velocity is more variable than expected, and

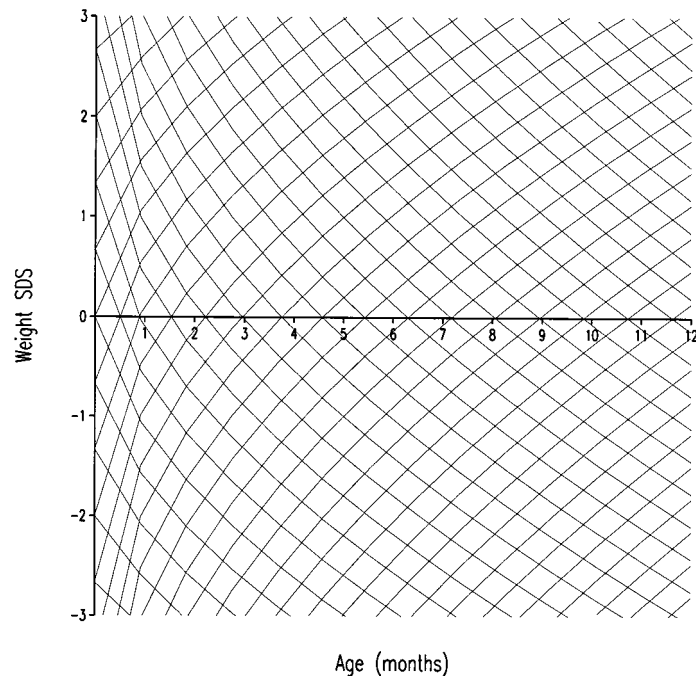


Figure 2. Weight SDS 5th and 95th conditional velocity centiles over 4 week periods in the first year. The lines are spaced two-thirds of an SDS unit apart at birth, and their slopes define the velocity centiles, which depend both on age and the starting weight SDS. The 5th centile lines fall and the 95th centile lines rise with increasing age

this leads to more than 5 per cent of subjects with velocities below the 5th centile. For longer intervals the opposite happens, and fewer than 5 per cent of subjects are screened in. The screening-in rate for different time intervals can be calculated in the following way: the rate of change in SDS associated with a 4-week 5th velocity centile can be extended over 8 or 12 weeks, and the actual change in SDS can be expressed as a conditional velocity centile in its own right.²² This is only possible for intervals longer than 4 weeks, as the Cambridge Infant Growth Study did not measure over shorter intervals.

For example, consider a 20-week infant on the 2nd weight centile growing parallel to the 5th centile for 8 weeks; expressing the start and end weights as a conditional velocity, using the 8-week correlation for age 20 weeks in Figure 1, gives a velocity SDS of -2.34 , on the 1st centile. Table II gives the screening-in rates for a series of ages and starting centiles over 8 and 12 week intervals. For 8 week intervals they are in the range 0.5–2 per cent, and over 12 weeks 0.1–1 per cent, with the lower rates at older ages and lower starting centiles.

DISCUSSION

The results show how to construct a growth chart which assesses weight centiles and changes in weight centile over time, while adjusting for regression to the mean. The chart is effectively a combination of three distinct forms of chart: distance; velocity, and conditional.²⁰ It builds on

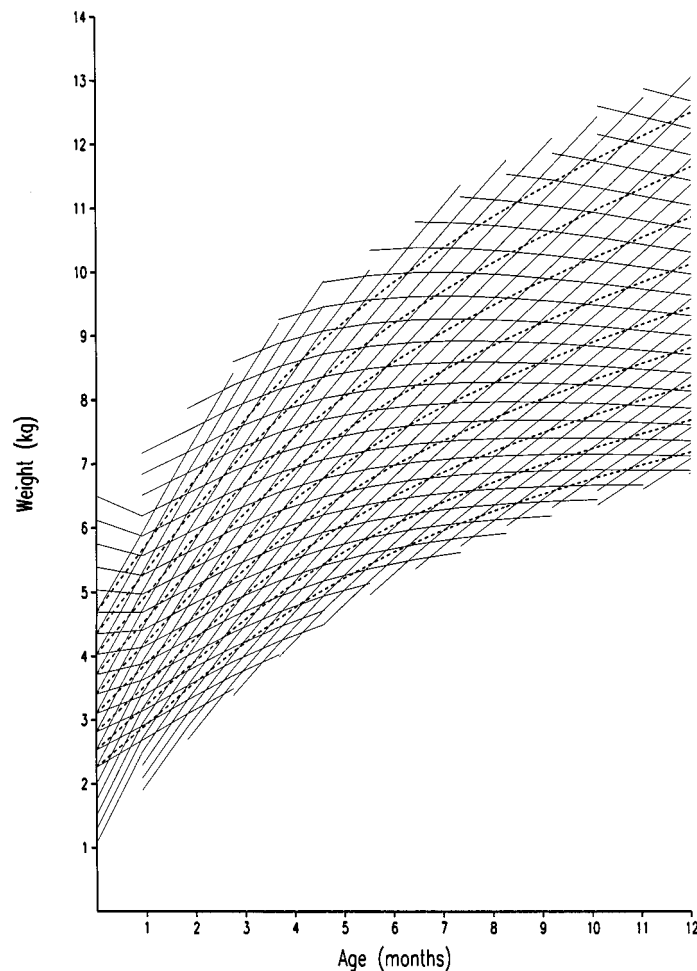


Figure 3. Weight 5th and 95th conditional velocity centiles for girls over 4 week periods in the first year (solid lines), superimposed on 9 distance centiles spaced two-thirds of an SDS apart, from the 0.4th to the 99.6th centile (dashed lines)

the idea of the Sheffield chart,²⁴ which was a weight distance chart with extra 'centile' curves spaced so that infants measured every 2 weeks had a 5 per cent chance of crossing (up or down) one channel width. The chart was designed for use with infants at risk of cot death, and this justified the high measurement frequency. The chart could also be used for 8-weekly measurements, where there was a 5 per cent chance of crossing two channel widths.

The concept of the Sheffield chart has recently been extended to adjust for regression to the mean.²⁵ The Wright chart focuses on centile crossing downwards, so the channels are progressively narrower from top to bottom. The chart is designed to monitor weight change over the longer period from 6 weeks to 12 months.

The problem with the Sheffield and Wright charts is that they express centile crossing in terms of channel widths, which can lead to practical difficulties in the choice of channel spacing at

Table II. Growing along the 5th conditional velocity centile for two or three 4-week periods. Conditional velocity as a function of age and starting centile

Weeks Age t	Distance SDS				Velocity t to $t + 8$		Velocity t to $t + 12$	
	at t	at $t + 4$	at $t + 8$	at $t + 12$	SDS	Centile	SDS	Centile
0	-2	-2.59	-3.04	-3.41	-2.28	1.1	-2.76	0.3
20	-2	-2.35	-2.68	-2.99	-2.34	1.0	-2.80	0.3
40	-2	-2.30	-2.60	-2.88	-2.49	0.6	-3.04	0.1
0	0	-1.06	-1.63	-2.09	-2.16	1.6	-2.55	0.5
20	0	-0.42	-0.81	-1.17	-2.34	1.0	-2.78	0.3
40	0	-0.35	-0.69	-1.01	-2.55	0.5	-3.11	0.1
0	2	0.48	-0.23	-0.77	-2.03	2.1	-2.34	1.0
20	2	1.51	1.07	0.65	-2.35	0.9	-2.76	0.3
40	2	1.60	1.22	0.86	-2.60	0.5	-3.17	0.1

different ages.²⁵ The alternative described here, using slopes of curves rather than distances between curves, is mathematically correct and is also more flexible. Thus the chart's design, particularly the chosen time interval and velocity centile, can be varied as necessary. The choices here, 4-week intervals and the 5th velocity centile, are intended to be practical but have no objective justification. It would be better to design the chart optimally.

However, first the assumptions behind the current chart need to be examined. The age-on-age correlations for weight SDS are treated as sufficient statistics for the corresponding conditional velocities, which assumes that weight SDS and conditional weight velocity SDS are distributed $N(0, 1)$. This can be tested with the Cambridge data. Mean weight SDS over the 16 ages was -0.09 (SD 0.10) and SD 0.98 (SD 0.03), the difference between successive 4-week means was within ± 0.06 past 12 weeks, and the ratio of successive SDs was within ± 0.03 of unity. Q-Q plots of the age-on-age regressions were remarkably linear, with consistently fewer than 5 per cent of points departing from linearity in the lower tail. So the 5th velocity centiles on the chart are generally unbiased.

The precision of the centiles is given by (8). When $r = 0.9$ for example, the slope of the 5th velocity centile on the SDS scale is -0.72 SE 0.045, while if $r = 0.97$ the slope is -0.40 SE 0.025. In both cases the t -value is -16.0 , so the centiles are estimated to high precision.

How to optimize the design of the chart is an under-researched area. The aim is to identify infants with a growth problem, so the chart is a form of diagnostic test. Such tests are validated by comparing two groups, one 'well' and the other 'ill'. The ability of the test to distinguish between the groups is summarized by the sensitivity, specificity, predictive values and ROC curve for the test. However, the methodology is difficult to apply to growth charts, largely because the 'ill' group is hard to define.

Healy³ proposed a two-stage monitoring scheme for short-term length increments. He tested its sensitivity by seeing how well it detected periods of growth faltering occurring at a random time. Thus his 'ill' group was subjects with a period of growth faltering. An alternative would be a longer-term definition of 'ill', a later diagnosis of illness for which growth faltering was a known precedent. 'Non-organic failure to thrive' (NOFTT) is one such diagnosis, and the Wright chart is designed to identify it. However, long-term weight loss is not only the diagnosis of NOFTT, it is also the main symptom, so unless there is other objective evidence for the diagnosis, the chart can

spuriously claim a sensitivity of 100 per cent. The growth patterns of cases with known aetiology other than NOFTT need further study.

An interesting feature of Healy's two-stage monitoring scheme is the use of three successive measurements. A sufficiently low velocity over the first interval leads to intervention, but if the velocity is borderline then the next velocity is taken into account. This approach improves both the sensitivity and specificity. An analogous procedure for the thrive line chart would be to assess weight velocity over the past 4 weeks, and if below the 5th centile then to assess the past 8 weeks. Table II shows that only 0.5–2 per cent of infants, depending on age and size, grow slower than the 5th centile thrive line for 8 weeks, corresponding to a specificity of 98 per cent or better, and this would have little effect on the sensitivity. Growing along the thrive line for 3 months or more is a rare event, and occurs mainly in young and heavy infants.

The slopes of the thrive lines depend on the weight SDS correlation structure, so to be generalizable the correlations need to be appropriate for community use. They were based on research quality measurements from the Cambridge Infant Growth Study (except birthweight, from hospital records), so the correlations may be on the high side. On the other hand, the Cambridge Study infants were screened by midwives before recruitment, and those thought to be at risk were excluded. For this reason the study population is likely to be unusually homogeneous, which would tend to *reduce* the correlations. Cole²² tested the correlations on Newcastle community weight data, and found the biases to be small.

The chart described here contains a lot of information, but even so it is seriously constrained to 4-week measurement intervals. The correct interpretation of the chart requires that the 4-week interval is understood by the user, and the chart design should emphasize this. One way would be to draw the velocity centiles in 4-week lengths, with alternating colours or line types, or else offsetting each length relative to its neighbours.

There are other ways the information could be handled, but not so conveniently. One possibility is a set of transparent overlays to put on the conventional distance chart, designed for different time intervals and/or velocity centiles. A sheaf of overlays would be needed to interpret individual charts. The other alternative is to computerize the conditional velocity calculation. By modelling the correlation structure between weights at different ages in the first two years of life (Table I), weight change over any time interval of 4 weeks or more can be assessed. For the assessment of three or more measurements, a multi-level model approach is required,²⁶ and software is being developed to assess multiple weight and height measurements throughout childhood.

Another format would be a thrive line chart with two velocity centiles, say the 5th and 95th, but no distance centiles (like the overlays described above). This would be a chart for infants with two or more measurements, and could be thought of as a form of 'Road to Health' chart.²⁷ It and the other design issues discussed here require validation in the field.

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