LONGITUDINAL AND CROSS-SECTIONAL REFERENCE CURVES OF GROSS MOTOR FUNCTION IN CHILDREN

By

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ABSTRACT

Reference curves are the most popular tool to monitor the time-related growth in children. Both cross-sectional and longitudinal studies are widely used to collect the reference samples. The methods used for constructing the reference curves and the interpretation of the curves for longitudinal studies should be different from those for the cross-sectional studies. However misunderstanding in constructing and interpreting the reference curves for the cross-sectional and longitudinal studies is common, especially the concerning of the effect of regression to the mean in the longitudinal studies. The LMS models of Cole and Green[1,2] using penalized likelihood are considered to be the most powerful methods to construct the reference curves for both cross-sectional and longitudinal studies. This thesis focuses on the comparison of the conditional LMS regression approach for drawing the median conditional centiles for longitudinal data to the conventional LMS model for constructing the distance centiles for cross-sectional data. It describes the different interpretations of the two approaches. The application of the two methods to a study of Gross Motor Function is investigated in detail to illustrate the difference between them.

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Chapter 1

INTRODUCTION

Reference curves have been widely used to illustrate the growth patterns of time-related data, especially as monitoring tools to identify deficits, for example delayed growth of children in height and weight[1,2,3]. Normally, a reference curves consist of a series of smooth curves which indicate the centiles of the distribution of the measurement - 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, and 95^{th}. The data, called the reference sample, which is used to draw reference curves, is usually collected from some pre-specified reference population. Cross-sectional and longitudinal studies are the two major study designs used to collect the reference samples. A cross-sectional study takes one observation from each subject in the given reference population at a given time, therefore the observations from a cross-sectional study can be assumed to be independent. A longitudinal study follows the same subject for a given period of time, often months, years, even decades. Each subject in this study will contribute more than one observation to the data set, and a positive correlation among the observations from the same subject exists. The correlation between observations is the main difference of the longitudinal study from the cross-sectional study. This is why a longitudinal study is also called a correlation study.

Many approaches for constructing the age-related reference curves have been developed. Cole and Green[1,2] developed the LMS model in 1992 using penalized likelihood to fit age-specific reference curves. The quantile regression method introduced b. Wei, et al[3] used the quantile specific autoregressive models to construct growth curves for unequally spaced measurements.

However, there are some misunderstandings on constructing and interpreting the reference curves for both cross-sectional and longitudinal studies. Theoretically, using same method to draw the reference curves for both studies is inappropriate, because of the correlation between the observations in a longitudinal study. The effect of the regression to the mean must be considered when analyzing reference curves for longitudinal study. Furthermore, when interpreting the centile curves, people usually assume that a subject always follows the centile at which he or she started at an early age. For example, they will assume that a child whose height is at 5th centile during infancy will always be around 5th centile when age increases; and a child whose height is at 95th centile will not come down to the median and should be always around 95th centile when age increases. But it is not true in most cases in practice. It commonly happens that a child who is higher than average during infancy is nearer the median height when being an adult, and vice versa.

To fix the problem, Cole developed a new method in 1994, called the conditional LMS model[1], to construct the median conditional velocity centiles for a longitudinal study. By applying the conditional standard to the z-scores of the measurement, the conditional LMS model successfully combined the effect of the regression of the mean to the median conditional centile curves and gave the appropriate interpretation of the median conditional centiles for a longitudinal study.

This paper focuses on the comparison of the conditional LMS centiles to the conventional cross-sectional LMS on the study of Gross Motor Function[4] in children with Cerebral Palsy and shows the different advantages of both approaches in interpreting children's movement disability situation.

Chapter 2

METHODOLOGIES

2.1 LMS Models and Maximum Penalized Likelihood

The LMS method was first presented by Cole and Green[1,2] to construct growth centile curves for the Fourth Dutch Growth Study. The key assumption of this method is that after a suitable Box-Cox transformation to the original data, the transformed data should follow a standard normal distribution. The L, M, and S in LMS individually indicate the Box-Cox power λ , the median μ and the standard deviation σ .

The LMS Method

Let y denote the variable of interest which has to be positive with median μ , and the Box-Cox power transformation of y is defined as

$$x = \frac{(y/\mu)^{\lambda} - 1}{\lambda}, \qquad \lambda \neq 0 \tag{1}$$

or

$$x = \log_e(y/\mu), \qquad \lambda = 0$$

where λ is the transformation parameter and the optimal value of λ can be obtained by minimizing the standard deviation of x. Let σ denote the standard deviation (SD) of x, the z-score of y is given by

$$z = \frac{(y/\mu)^{\lambda} - 1}{\lambda\sigma}, \qquad \lambda \neq 0 \tag{2}$$

or

$$= \frac{\log_e(y/\mu)}{\sigma}, \qquad \lambda = 0$$

by assumption, z has a standard normal distribution.

Next, assume the distribution of y is associated with time t, typically age t. Let curves L(t), M(t) and S(t) denote λ , μ and σ at time t , then the z-score at time t is written as

$$z = \frac{[y/M(t)]^{L(t)} - 1}{L(t)S(t)}, \qquad L(t) \neq 0 \tag{3}$$

or

$$z = \frac{\log_e[y/M(t)]}{S(t)}, \qquad L(t) = 0$$

rearranging (3), the 100α centile of y at time t is obtained as

$$C_{100\alpha}(t) = M(t)[1 + L(t)S(t)Z_{\alpha}]^{1/L(t)} \qquad L(t) \neq 0 \tag{4}$$

or

$$C_{100\alpha}(t) = M(t)Exp[S(t)Z_{\alpha}] \qquad\qquad L(t) = 0$$

where L(t), M(t) and S(t) (or L, M and S) are also called parameter curves. Note that if L(t), M(t) and S(t) are smooth, so are the centile curves.

Maximum penalized likelihood

Let l denote the log-likelihood function of n independent observations y_i, $i = 1, \ldots,$ n at time t_i. The log-likelihood function is obtained from (3) as

$$l = l(L, M, S) = \sum_{i=1}^{n} \{L(t_i)\log\frac{y_i}{M(t_i)} - \log[y_i S(t_i)] - \frac{1}{2}z_i^2\} \tag{5}$$

where z_is are the z-score of y_is. The penalized likelihood is given by

$$l - \frac{1}{2}\alpha_\lambda \int\{L''(t)\}^2 dt - \frac{1}{2}\alpha_\mu \int\{M''(t)\}^2 dt - \frac{1}{2}\alpha_\sigma \int\{S''(t)\}^2 dt \tag{6}$$

where α_λ , α_μ , and α_σ are smoothing parameters or the degrees of smoothing. The degrees of smoothing can also be specified by equivalent degrees of freedom (edf) for the fitted cubic spline curves L(t), M(t) and S(t). For given pre-specified equivalent degrees of freedom values of the three curves, the optimal smooth curves L(t), M(t) and S(t) can be estimated by maximizing the penalized likelihood.

The degree of smoothing can be defined either by α or by equivalent degrees of freedom (edf). The definition of the three parameters is given in the paper of Cole and

Green[2]. They discuss that either approach is feasible for fitting the model, but using edf is more convenient in practice, and this option is used by the corresponding R package – lmsqreg() for fitting the LMS model.

The Determination of Equivalent Degrees of Freedom

The equivalent degrees of freedom (or called degrees of smoothness) of the three parameter curves are the only parameters for LMS model, therefore the major modeling task becomes to identify the appropriate amount of smoothness of each curves. Let E_L, E_M, and E_S denote the edf of the three parameter curves L, M and S in the LMS model, while the complexity of the three smooth curves can be characterized by the numbers E_L, E_M, and E_S. Theoretically, E_L, E_M, and E_S are non-negative integers. By definition, when the degree is 0, the smooth curve is fitted by a fixed value; when the degree is equal to 1, it is fitted by a constant value; when the degree is 2, it is linear fit; when the degree is 3 or more, the smoothing is performed. Cole suggests that among the three parameters, because the M curve describes the most important variation, the sequence of choosing the optimal values of edf for the three curves should be M first, and then S, and then L. He explained that the three parameters are largely independent of each other, implying that one edf can be optimized while fixing the other two. As following the procedure introduced by Cole[6], in order to optimize E_M, starting from $E_M = 4$ and $E_L = E_S = 1$, one can progressively increase E_M by 1 until the change in the penalized likelihood becomes so small that the test statistic for the change shows a non-significant result at the 5% significant level. Typically, the change is measured by the *D-statistic*, defined as $D(l_1, l_2)$

$= -2(l_1-l_2)$, where l_1 is the penalized likelihood of the model with less degrees of freedom nested inside the model 2. The *D-statistic* has an asymptotic chi-squared distribution with degree of freedom d, where d is the number of parameters in model 2 minus the number of parameters in model 1. The *D-statistic* is calculated to test the significance of the change at the 5% significance level. After E_M is determined, we fix E_M at the optimal value, and follow the same strategy to optimize E_S, and then keep E_M and E_S at optimal values, to find out the best value of E_L.

2.2 Conditional LMS for longitudinal data

The motivation for the conditional LMS model[1] is to take account of the effect of regression to the mean of the reference curves for longitudinal data. To reach the goal, a 'conditional standard' model is introduced. Let Y_t denote the variable of interest at time t, and Y_{t-1} at time t-1, then the regression-based conditional standard can be defined as,

$$Y_t - b_t Y_{t-1} = c_t + \varepsilon$$

where b_t is the regression coefficient and c_t is the regression intercept, and the residual has normal distribution N(0, σ_t^2). The left side of the equation is also called the 'conditional velocity' as opposed to the ordinary velocity $Y_t - Y_{t-1}$, which is uncorrelated with Y_t by definition. Therefore, the conditional velocity is expected to be same at any particular age. Note that the regression to the mean happens when b_t is less than 1.

The conditional standards can be applied to the z-scores which are calculated from the original data. Note that when the original data are normally distributed, the two approaches are algebraically identical. But when the original data is skewed, using a normally distributed z-score is more convenient. The conditional standard of z-score at time t can be defined as,

$$Z_t = r_t Z_{t-1} + \varepsilon \tag{7}$$

where r_t is the correlation between Z_t and Z_{t-1}, and for some reasonable sample size n_t the residual standard deviation is assumed to be distributed N(0, 1 - r_t^2), therefore the conditional velocity z-score Z^* is given by

$$Z^* = \frac{Z_t - r_t Z_{t-1}}{\sqrt{(1 - r_t^2)}} \tag{8}$$

rearranging (8), for a given z-score at time t-1, the 100α conditional velocity centile of z-score at time t is given by

$$Z_t = r_t Z_{t-1} + \sqrt{(1 - r_t^2)} Z_\alpha^* \tag{9}$$

where Z_α^* is the normal equivalent deviate (NED) of size α. $Z_{0.5}^* = 0$ corresponds to the median z-score velocity, $Z_{0.95}^* = 1.64$ corresponds to the 95th centile and $Z_{0.05}^* = -1.64$ to the 5th centile. Finally, the conditional velocity centiles can be obtained by replacing Z_α in (4) by the new Z_t derived from (9).

2.3 Model Diagnostic

For a given choice of E_M, E_L, and E_S, the LMS program maximizes the penalized likelihood to estimate the smooth curves L(t), M(t) and S(t). If the model fits well, the SD scores should follow a standard normal distribution N(0,1) at all ages, so by testing the normality of z-scores, the quality of the model can be diagnosed. Among all available diagnostic methods, quantile-quantile plot (Q-Q plot) is best-known due to its easy applicability to show structural characteristics, such that the skewness and kurtosis, therefore it was chosen to be the tool to test the quality of LMS model in this study.

Chapter 3

MOTOR DEVELOPMENT STUDY IN CEREBRAL PALSY

3.1 The Gross Motor Function Classification System for Cerebral Palsy

Cerebral Palsy (CP), a permanent physical disability that affects movement, and occurs in every to 2/1000 to 2.5/1000 live births[4]. The Gross Motor Function Classification System for Cerebral Palsy, first developed by McMaster University – Centre for Childhood Disability Research, was designed by using principles of classical test theory to classify the level of the children's present abilities and limitations in motor function. The system defines 5 severity levels to distinguish significant functional disabilities, where Level I is the most functional and Level V is the most limited. The level scale is ordinal, but this does not mean that the distance between the levels is equal or that children with CP are equally distributed among levels. More detailed description of functional abilities at each level can be found on the study website www.fhs.mcmaster.ca/canchild. The Gross Motor Function Measure-66 (GMFM) is a measurement with a scale from 0-100 score to indicate the movement abilities of a person, where a higher score means more movement ability and a lower score means less movement ability. GMFM is based on 5 functional dimensions: (1) lying and rolling; (2) sitting; (3) crawling and kneeling; (4) standing; and (5) walking, running, and jumping. It has recently been used world wide as a clinical and research outcome measure for children with CP.

The Gross Motor Function Classification System and the Gross Motor Function Measure are two separate systems. The former is designed for the children with cerebral palsy to identify the severity level of their movement disability, but the later is using the 0-100 score to indicate the children's motor functional abilities and theoretically can be used to anybody. The Gross Motor Function Measure[4] included 88 test items on 5 functional dimensions when it was first designed, but it was later reduced to 66 items, so GMFM-66 is used to indicate the revised GMFM. The data used by this article is based on 66 items test. Both GMFM and GMFM-66 are used to denote the same score in this paper. It is well known that normal children rapidly improve their movement ability with their growing from age 1 to 12, so the children at different ages will have significant differences in their movement behaviors. This is also true for the children with CP. To describe the functional abilities of the children at different ages, 4 age strata are pre-defined: (1) before 2nd birthday, (2) 2 to 4th birthday, (3) 4 to 6th birthday, and (4) 6 to 12th birthday.

3.2 Study Description

In 1996, McMaster University CanChild Centre for Childhood Disability Research conducted a multi-centre longitudinal cohort study of children with CP. The purpose of the study was to display the patterns of gross motor development of children with CP at age 1 to 13 and provide a basis of prognostic consulting for parents and doctors, and to make the management of future clinical therapy. The study measured the GMFM scores of a total of 657 children with CP aged 1 to 13 years for the period from 1996 to 2001. The reference samples collected from 18 centers and 1 hospital-based therapy program in Ontario were stratified by age and severity of motor function.

3.3 Sample Description

2609 GMFM66 scores were taken from 657 patients during the 5-year study period. Each patient had 3-6 distinct observations. Theoretically, every observation for the same patient should be taken at different year to make the data evenly distributed in time. The advantage of doing this is to give the same weight to each patient for each age interval in the model. However, it is hard to reach the optimal solution in reality. It happens that for the same patient there is more than one observation within a 12 month interval. To solve the problem, one observation is randomly taken if there are two or more observations within 12 month for the same patient. At the end, a total of 2176 observations were selected for further analysis.

	N	Median	Mean	SD
Level I	609	84.50	82.57	11.48
Level II	287	65.33	64.50	10.95
Level III	428	52.09	51.79	7.54
Level IV	436	39.73	39.80	7.68
Level V	416	22.66	23.69	7.92
Total	2176			

Table 1: Sample Distribution of Gross Motor Function Study

Table 1 lists the selected sample size and the mean, median and standard deviation in each level. Note Level I has the biggest sample size, and Level II has the smallest sample size. The histogram plots in Appendix D give more visible picture of the data distribution in each level, where the data in Level I and IV are right skewed but still looks normal, and the data in Level II, III, and V are roughly normal. It satisfies the assumption of LMS method that the underlying distribution of the data should be normally skewed distributed (see Chapter 2).

Chapter 4

RESULTS AND DISCUSSIONS

4.1 Cross-sectional LMS centile curves

Figure 1 shows the GMFM66 cross-sectional LMS regression centile curves (or distance centile curves) for Level II. Appendix A gives the corresponding centiles for the other four levels. Figure 1 includes four different graphs. The top three small graphs are the smoothed curves of *L*, *M* and *S* against age, where Lambda (λ) in the top-left graph is the Box-Cox transformation parameter required to remove the skewness, Mu (μ) in the top-middle graph indicates the median GMFM66 score, and Sigma (σ) in the top-right graph is the coefficient of variation. The big graph at the bottom shows the 5th, 10th, 25th, 50th, 75th, 90th, and 95th centile curves with edf = (1, 4, 1) for Level II.

Figure 1 shows that the lambda value of Level II increases initially, and then decreases to 0.04 after it reaches its maximum value 0.42 around age 7. The change in lambda shows that the skewness shape switches with ages. In this case the peak of skewness curve switch slightly to the right with ages at the beginning and then switch back after age 7. There is a monotonic increasing trend in the median GMFM score in Level II with ages. However, the rate of improvement is greater between ages 2 - 9, when the median

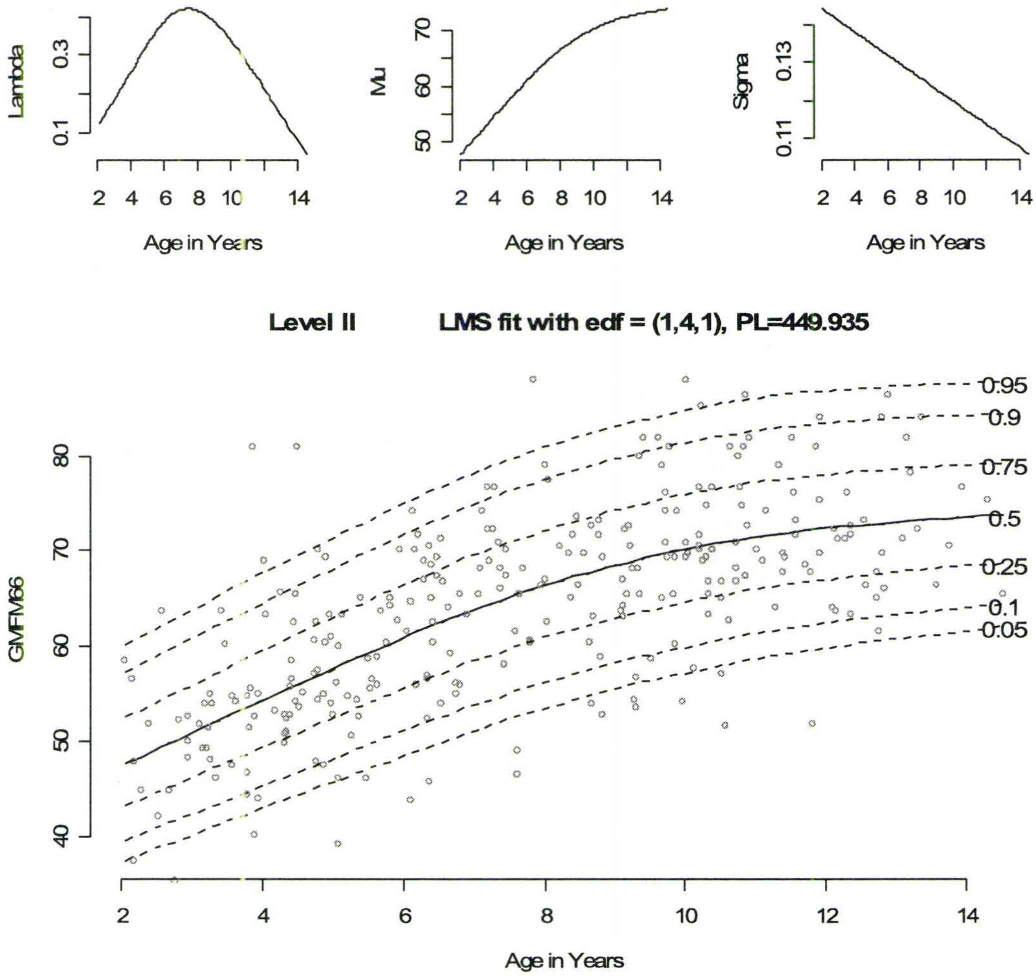

Figure 1: The fitted GMFM66 cross-sectional LMS regression centile curves and the smooth curves of *L*, *M* and *S* for Level II

GMFM score increases from 47 to 67. After age 9, the rate of improvement slows down, and the change of the median GMFM score is from 67 to 73. The coefficient of variation monotonically decreases through all ages, from 0.14 to 0.11, meaning that the movement abilities of children in this level varies more at younger ages and become slightly less variable at later ages, but the variability is very small compared to the corresponding median values so that the different variability at different ages is hardly seen from the centile curves graph. The big graph in Figure 1 shows 7 smooth curves at 5th, 10th, 25th, 50th, 75th, 90th, and 95th centiles, where the small circles are the original GMFM66 scores on various ages. The data is slightly right-skewed at all ages, as seen by comparing the distance from the lower and upper centiles to the 50th centile, but the effect of skewness at different ages isn't obviously noticeable from the graph. The change in the coefficient of variation at different ages is significantly small that no important effect can be seen from the centiles graph.

Figure 1 in Appendix A shows the cross-sectional LMS centile curves of Level I. The lambda values in Level I are very variable compared to those for other levels. They increase monotonically with ages from 1.05 to 4.31. The median GMFM66 score increases sharply from about 58 to 86 between ages 2 and 8, but the speed of the increment slows down after age 8 and finally there is no substantial increment after age 10, which indicates that the median children in Level I achieve their maximal functional abilities mostly before 8 years old. After 8, the improvement in their functional abilities is quite limited, and when they are older than 10 years, they may not experience any further improvement. The coefficient of variation in Level I roughly decreases with age, but as for Level II, the range is very small, only 0.08 - 0.12. The distribution of GMFM scores against age for Level I is shown by the 7 cross-sectional centile curves. Interestingly, the graph displays left-skewed distribution of GMFM scores after 8 years of age, which shows that more children tend to be close to or better than the median in this age group. The effects on GMFM score of varied skewness and variation at different ages are clearly seen from the graph in this level.

The cross-sectional LMS centile curves of Level III are shown in Figure 2 in Appendix A. In this level, the power (λ) needed to remove the skewness decreases at first, and then increases slightly after age 10, ranging between 1.28 to 1.97. The median GMFM score ranges from about 42 to 53, with the greatest increment being between age 2 to 7. After age 7, the average movement abilities will be slightly lost as the children get older. The coefficient of variation monotonically increases from 0.12 to 0.18 with age. The effects of the increase of the coefficient of variation can be clearly seen from the cross-sectional centile curves in this level. The distribution of GMFM scores becomes more variable as age increases. The median score doesn't vary too much from age 2 to 14 in this level, but the distance between the two extreme centiles, the 5th and 95th, is greater at age 14 compared to age 2. That means that the functional abilities vary substantially when the children grow up in level III. Some may behave much better than expected, but others may be much worse than expected.

The graphs for Level IV are shown in Figure 3 in Appendix A. The behavior of the lambda values against age in Level IV is very different compared to the other 4 levels. Lambda increases from about age 2 to 6, reaching its highest value 2.43 at age 6, and then decreases to its lowest value 0.81 around age 11, after which it starts to increase again. The distinctive behavior of lambda values has a visible effect on the centiles. Note that the wilder spread of centile curves around age 6 can be explained by the skewness around this age. The median GMFM score increases from about 32 to 42 between age 2 and 7, but after age 7, the average movement abilities decline. The coefficient of variation increases from 0.15 to 0.21 with age. Because the change in the median score is small, (only about 10), the 7 centile curves are quite constant with ages. The children in this level do not improve very much as they grow up.

Similarly to Level III, the skewness parameter in Level V decreases at first, and then increases slightly after age 10, ranging between 0.62 and 1.11, shown by Figure 4 in Appendix A. The children in Level V have the greatest limitations on their movement functions. The highest median GMFM score is only about 25, achieved when the children are about 7 years old, and after that they may lose some movement functions. There is a difference of only 5 points on the GMFM score between the highest and the lowest medians, and the children in this level hardly have any improvement at the median level. The coefficient of variation increases with ages. The effect of the increasing variation with ages is evident from the spreading of distance between centiles at larger ages. The centile curves in Level V are the most constant among the curves of all levels.

Overall, the graphs show that the children with the lowest severity of CP will be the most likely to improve their movement abilities, such that the children in Level I have the biggest probabilities to improve their functional behavior, and the children in Level II have less probabilities compared to Level I in developing their movement, Level III to V follow the same rule. However, the charts also show that for the children in Level I and II, they may experience significant improvement on their movement abilities, but for the children in Level III and above, their improvement is very limited, and furthermore the children in Level IV and V almost have no improvement at all during infancy and puberty. The most speedy improvement period of the movement abilities for all children is before 7 no matter which level they belong to, and after 7 the speed of improvement slows down, particularly the median growth becomes negative for Level III to V.

The effect of skewness parameter varied between 5 levels. Its effect on the graphs in Level IV is more obvious than in the other 4 levels. The scale of the coefficient of variation and its range have the increasing trend from Level I to V, which means that the higher level has wider variance than lower level with ages. The coefficients of variation roughly decrease with age in Level I and II, but follow the same increasing pattern with age in Level III to V, the increment in variance against age can be obviously seen in the graphs of the three levels.

Finally, the five levels' cross-sectional centile curves show the overall distribution of the GMFM66 scores with ages for the children with CP by severity, and express the patterns of the development of the children's movement abilities against ages by severity levels. In clinical practice, they are the important prognostic tools for doctors and parents on identifying a new patient's severity and planning a reasonable clinical management.

4.2 Model Parameters Determination

As suggested by Cole[6], we start from $E_M = 4$ and $E_L = E_S = 1$ for all levels, and progressively increase the E_M value by increments of 1 while keeping E_L and E_S fixed, and we test the *D-statistic* until the change is so small that *D-statistic* is not significant at 5% confidence level. Once E_M has been chosen, we determine E_S next, and then E_L at the end following the same strategy as for determining E_M. Table 2 shows the final model parameter values for five levels.

	E_L	E_M	E_S
Level I	1	5	1
Level II	1	4	1
Level III	1	5	1
Level IV	1	5	1
Level V	3	4	1

Table 2: Model parameter values for Level I to V

4.3 Model Diagnostics

The LMS model assumes if the model fits well, the z-scores should follow a standard normal distribution at each age. A Q-Q plot of the z-scores of GMFM66 is

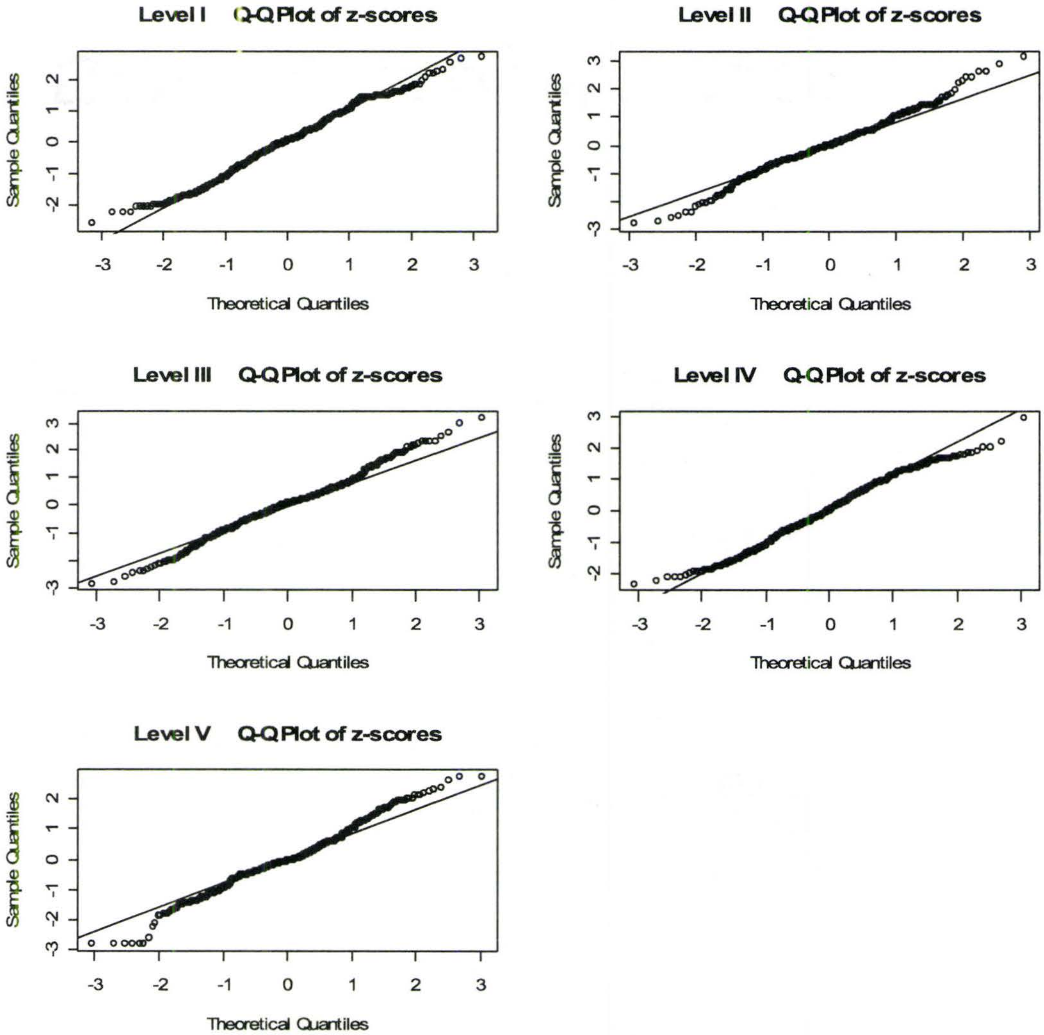

Figure 2: Normal Q-Q plot of z-scores for Level I to V

drawn to diagnose the quality of the fit. Figure 2 gives the Q-Q plots of the z-scores for Level I - V. Overall the z-scores of GMFM66 at all levels are approximately normally distributed. When compared to the histogram of original GMFM66 scores shown by Figure 1 in Appendix C, we conclude that the LMS model effectively reduces the skewness and the variation of the original data, and each of 5 models is acceptable.

4.4 Median Conditional Velocity Centiles using Conditional LMS

Above is the analysis of the centile curve using the cross-sectional LMS model. Now, we move to the major part of this paper – the median conditional velocity centile curves using the conditional LMS model on longitudinal data.

Correlation between SD scores at time *t* and *t*-1

To obtain the conditional standards at all ages, the correlation between the z-scores of GMFM66 at time *t* and *t*-1 are calculated for all levels. Figure 2 shows the plots of correlation values versus age for each of five levels. Note that the correlation at age 8 in Level II is remarkably low, less than 0.4, which may be due to the small sample size at that age. This kind of problem exists elsewhere, such as at age 4 in Level III and age 3 in Level IV. To fix this problem, a simple linear regression of the correlation values against age was fitted, weighted by the corresponding sample size. The fitted regression line is shown in Figure 2 for all 5 levels. The fitted correlations in Level I, II, and IV are very constant at all ages, but in Level III and V, the fitted correlations have an increasing trend along with ages. Table 3 gives the fitted correlations at each age for 5 levels.

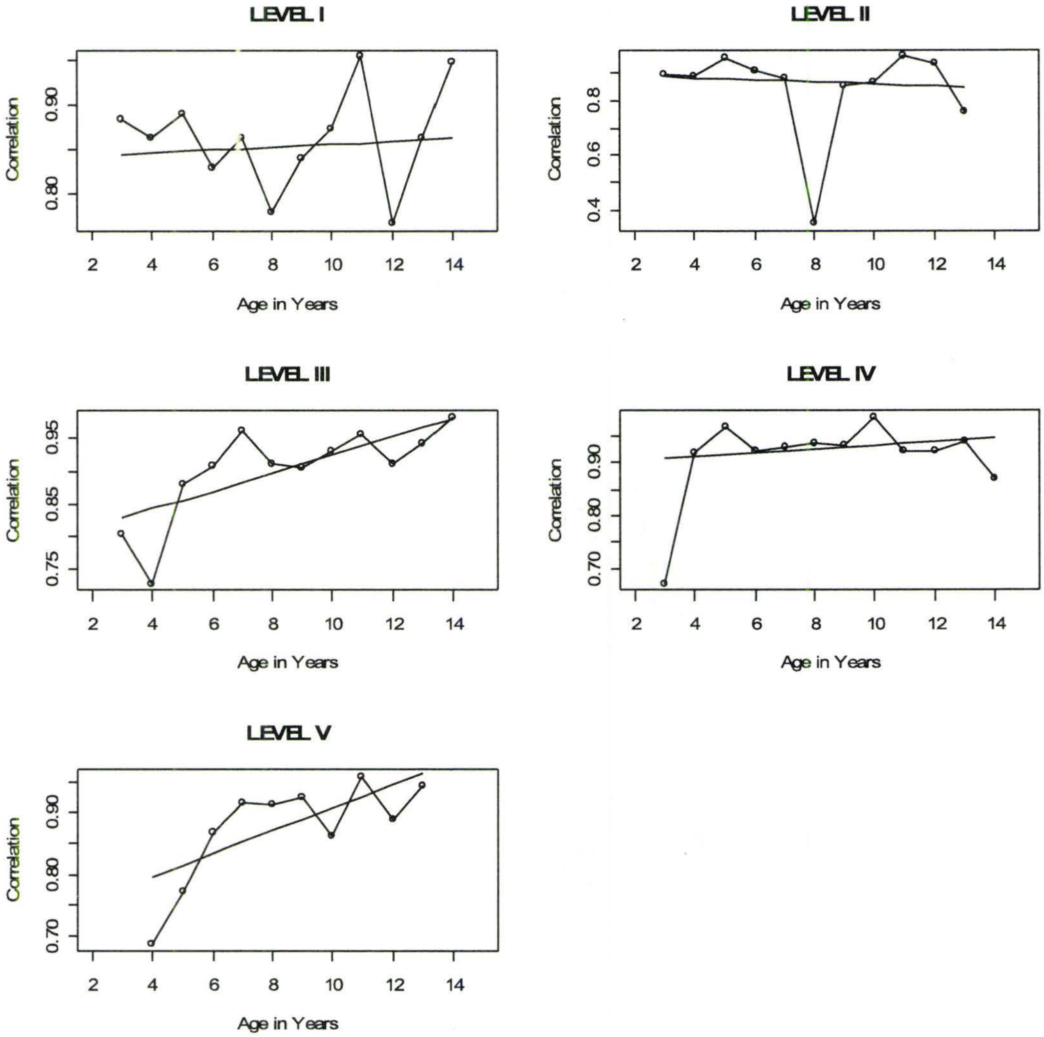

Figure 3: Correlation between SD scores of GMGM66 at year t and t-1 for Level I-V

Table 3: The fitted correlations at each age for Level I to V

	Level I		Level II		Level III		Level IV		Level V	
Age	n1	Corr.	n2	Corr.	n3	Corr.	n4	Corr.	n5	Corr.
3	12	0.843	6	0.884	10	0.825	7	0.918	4	NA
4	16	0.844	18	0.881	17	0.839	12	0.920	14	0.797
5	30	0.846	25	0.878	19	0.854	23	0.923	26	0.815
6	48	0.848	19	0.875	23	0.868	31	0.925	29	0.834
7	42	0.849	15	0.872	18	0.882	28	0.928	27	0.852
8	39	0.851	11	0.869	27	0.896	20	0.931	25	0.870
9	35	0.852	14	0.867	34	0.910	25	0.933	29	0.889
10	32	0.854	23	0.864	32	0.924	36	0.936	34	0.907
11	37	0.856	23	0.861	33	0.939	30	0.938	26	0.926
12	44	0.857	21	0.858	26	0.953	29	0.941	22	0.944
13	37	0.859	14	0.855	19	0.967	20	0.943	12	0.963
14	20	0.860	4	NA	15	0.981	8	0.946	5	NA

Median Conditional Velocity Centiles

By definition, the median conditional velocity centile in this case is the predicted median GMFM66 score for childen at age t. Let $Z_{0.5}^{*} = 0$, given r_t and the starting value of Z_0, the Z_t $(t = 1, 2, \ldots)$ in (9) is calculated sequentially. We convert the calculated Z_t back to (4), and the median conditional velocity centile can be obtained. The starting value of Z_0 corresponds to the starting value of the median conditional velocity centile curve at time 0. In fact, the median velocity centile can be started from any time t-1. If t-1 = 4, then the median velocity centile displays the median GMFM66 score starting at age 4 until the end of follow-up.

Figure 4 shows 7 median conditional velocity centiles (solid lines) starting from age 2 in Level I, where the 7 dashed lines are the cross-sectional centile curves of this level. The two kinds of centiles give a clear view of how different the median conditional velocity centile predict the children's movement ability years later against the cross-sectional centiles when both centiles start from same value at age 2. There is an obvious

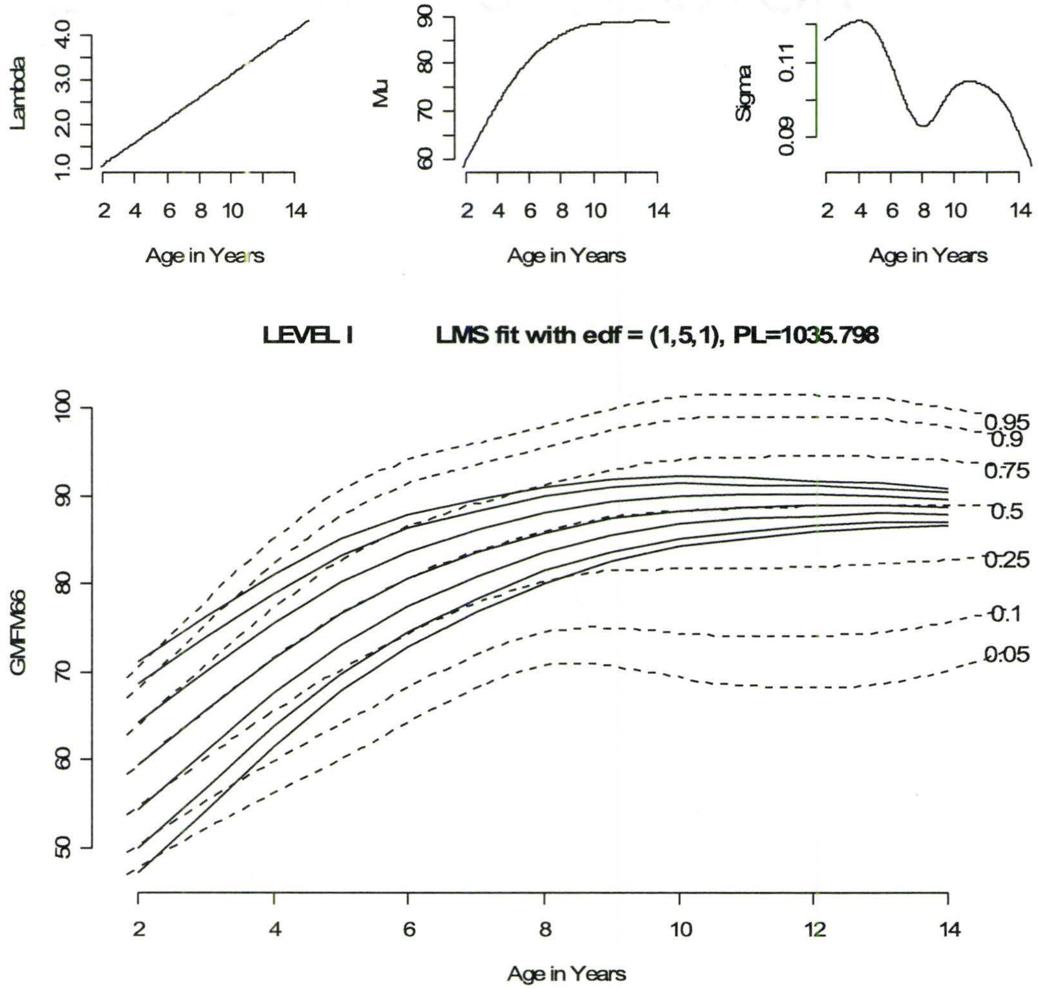

Figure 4: Cross-sectional LMS regression centile curves (dashed line) vs. median GMFM66 conditional velocity centiles (solid lines) for Level I

trend from the graph that the median conditional centile catch up crossing the distance centiles to the 50th cross-sectional centile when it start lower than the median, and fall down crossing the distance centiles to the 50th cross-sectional centile when it start higher than the median. The first solid line from the top can be explained that a child's predicted median GMFM score that is at relatively high level at age 2, as his or her GMFM66 score at age 2 is at the 95th cross-sectional centile, will gradually go down to the median level as long as the age increases. Contrarily, the bottom solid line can be interpreted that a child's predicted median GMFM score that is at relatively low level at age 2, as his or her GMFM66 score at age 2 is at the 5th cross-sectional centile, will gradually catch up to the median level as the age increases. This is the key difference between the median velocity centiles and the centiles from the cross-sectional analysis, the latter assumes that the children in an upper centile at early age should mostly stay on as the age increases, or that children with most limited movement function have a high probability to be in the lower centile at older ages. In fact, this is not true in reality. The effect of regression to the mean should be taken account when dealing with the same person for a long period of time. Moreover, the median GMFM scores of children with more extreme high or low starting GMFM scores change more than of those nearer the 50th cross-sectional centile. Also note that the median velocity centile starting at the 50th cross-sectional centile is parallel to the 50th cross-sectional centile.

Figure 1 to 4 in Appendix B give the median conditional velocity centile curves vs. cross-sectional centiles for Level II to V. All the median conditional centiles have the same pattern such that the median conditional centiles catch down or up crossing the distance centiles to the 50th cross-sectional centiles in all levels. The only difference is the different velocity of crossing the distance centiles in each level. Note that the median velocity centiles move faster toward the 50th cross-sectional centile at all ages in Level I and II compared to other levels. By looking at the formula (9), it is easily seen that the new Z_t is partly determined by the value of the correlation at time t, such that a smaller correlation at time t results in a smaller Z_t. The equation (4) shows that a smaller value of Z_t gives a steeper change in the median velocity centile to the 50th cross-sectional centile at that time, if L(t) and S(t) are constant at all ages. In Levels I and II, the correlations are smaller at all ages, around 0.85 in Level I and 0.87 in Level II (see Table 2) than those in Level III to V, where as in Level III the increasing correlations against ages from 0.826 at age 3 to 0.981 at age 14 make the median velocity centile change more steeperly at early ages, and then the changes get smaller as age increases. The effect of changes in correlations along the ages at Level III can be clearly seen in Figure 2 in Appendix B. In this case the changes in L(t) and S(t) are so small that they have limited effects on the changes in the median velocity centiles. The effect of correlation in Level V is similar to those in Level III (seen Figure 4 in Appendix B). The median conditional velocity centiles in Level III change more steeply at early ages, and gradually the changes get smaller and smaller as age increases so that the centile curves look more parallel at later ages than early ages. Specifically, the correlations in Level IV are close to 0.93, so that the speed of crossing the cross-sectional centiles of the median velocity centiles in

Level IV is much slower than those in other levels. Figure 3 in Appendix B clearly shows these features.

In clinical practice, the children with CP seeing a doctor are at all ages, so it is very important for a doctor to predict a child's median behavior based on each patient's individual age. Figure 5 to 9 in Appendix B show the median conditional velocity centile curves for Level II to V with the median conditional velocity centiles starting at different ages. Next, the conditional velocity centiles for a distinct child are developed.

4.5 Conditional Velocity Centiles for a Particular Child

In reality, it happened frequently that the doctor and parent of a child with CP want to predict what is going to happen to the child several years later, and whether he or she might perform better or worse than expected. If we let Z_{α}^{*} be -1.28, -0.67, 0, 0.67, and 1.28 in (9), the conditional 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th} velocity centiles can be drawn. Figure 5 gives 5 velocity centile curves of a 4 years old child in Level I whose GMFM66 score is 70. Theoretically, the 90th centile curve gives the child's predicted GMFM66 score when assuming this child always behaves better than average at the 90th centile level after age 4, and the 10th velocity centile curve is assuming that this child always behaves lower than average at the 10th centile level after age 4. The 50th velocity centile gives the child's median change of GMFM score.

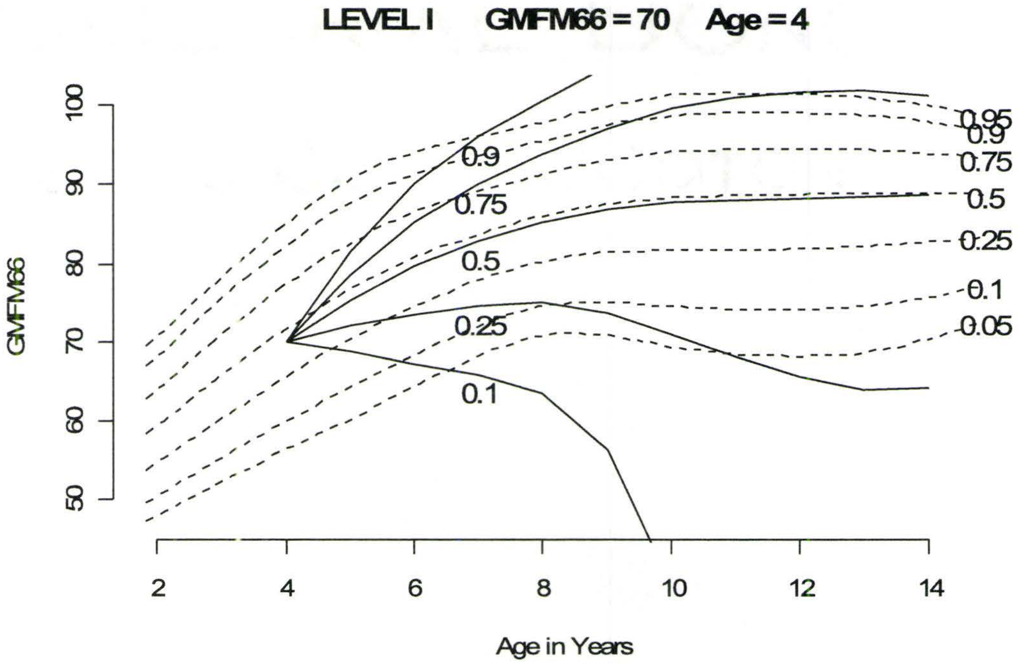

Figure 5: Cross-sectional LMS regression centile curves (dashed lines) vs. conditional velocity centiles (solid lines) for a child starting at age **4** and GMFM66 **70** in Level I

Note that the 5 conditional centile curves spread out rapidly. In fact it can't be real that a child will always follow 75% centile or 90% centile for several continuous years. As this chart is based on one year ahead prediction model which means that the later year's value is predicted by the previous year's value, we concluded that this chart is more useful and accurate for 1 or 2 years ahead prediction then 3 or more years' prediction. However, the chart still shows us the pattern of the change theoretically.

Figure 1 to 4 in Appendix C show an example of 5 conditional velocity centiles in Level II to V - age 3 with a GMFM66 score of 55 in Level II , age 6 with a GMFM66 score of 42 in Level III, age 5 with a GMFM66 score of 42 in Level IV and age 7 with a GMFM66 of 25 in Level V. Note that the 5 conditional centiles spread out rapidly for all examples, no matter what is the starting point; the 90th conditional velocity centile is extremely high and the 10th conditional velocity centile is extremely low several years later after the starting year, that both of them are out of the range as shown in the plots. However, it rarely happens in reality that the child always follows the 90th centiles or 10th centile for all ages. The relation in percentage change from t to t+1 against the change from t+1 to t+2 is a useful tool to see whether exists a common rate of changes among different time ts. Figure 2 - 6 in Appendix D plots the predicted change from t to t+1 against the change from t+1 to t+2 for all levels, and clearly shows that the percentage changes are randomly distributed at all ages so that there is no common trend in the percentage change for all patients. From this point of view, focusing on the median change is more informative.

4.6 Evaluation of Conditional LMS Model

To test the quality of the conditional LMS model, the difference of the true score a year ahead minus the predicted GMFM66 scores a year ahead and its standard deviation are calculated for 5 levels (see Table 4). The coverage of the 95% prediction interval shows how well the model performs at each level. Apart from Level II, the means of errors are positive in all levels, which indicates that the predicted score a year ahead tends to be smaller than the corresponding true score. However the errors are so small compared to the standard deviation of the errors that the trend can be ignored and the small errors show the good fitting of the model. The coverage probabilities of 95% prediction intervals for Level I and II are very close to 0.95, Level III has the lowest coverage 0.908. Overall, the coverage probabilities are all above 0.90, which indicate that the conditional LMS model fits well in all levels. Table 1 in Appendix D gives the distribution of differences at all specific ages.

Level	N	Mean of Err.	Sd of Err	Coverage of 95% PI
1	389	0.211	4.745	0.941
2	189	-0.144	4.082	0.947
3	273	0.457	3.000	0.908
4	269	0.195	2.826	0.925
5	244	0.491	3.654	0.922

Table 4: The distribution of (y - predicted.y) a year ahead for Level I to V.

Chapter 5

CONCLUSIONS

This paper shows how different the conditional LMS models are in expressing different aspects of the centile curves compared to the cross-sectional LMS model on the GMFM scores for children with Cerebral Palsy and how the regression to the mean affects the behavior of the median conditional centile curves in the conditional LMS model.

Basically, the cross-sectional centiles show us the overall distribution of the GMFM score against age, including the median GMFM score at any given age and the corresponding distribution adjusted by the skewness and the coefficient of variation at that age. In clinical practice, the advantage of using the cross-sectional centiles is to help the doctors to decide what percentage a new patient is at according to the distribution at his or her age by severity level and to identify whether the patient is extremely better or worse than normal. It is very important tool to help the doctors to assign a reasonable treatment for this patient and help the parents to understand the situation of the child and possibly provide a positive support to the doctors' management.

However, the conditional centiles are better at predicting the median behavior of a certain patient one or several years later than the corresponding cross-sectional centiles. By taking account of the regression to the mean in the longitudinal data, the conditional LMS centiles focus on describing the single patient's development at a year and several years later according to the current situation of this patient, especially the median behaviors of this patient at later ages no matter what the status of the other patients. This is useful in clinical practice when the doctors and parents are more interested in the later development of a child. The results show that a child with the GMFM66 score lower than the median (the 50^{th} cross-sectional centile) will catch up to the median with age due to the regression to the mean if the child follows his or her median conditional centile; conversely a child with the GMFM66 score higher than the median will fall close to the median with age due to the regression to the mean if the child follows his or her median conditional centile.

Another important aspect is that the velocity of the median conditional centile crossing down or up the distance centiles is partly affected by the correlation in z-scores. The low correlation results in a high velocity of crossing down or up the distance centiles, and the high correlation results in a low velocity of crossing the cross-sectional centiles.

APPENDIX A

CROSS-SECTIONAL LMS CENTILE CURVES

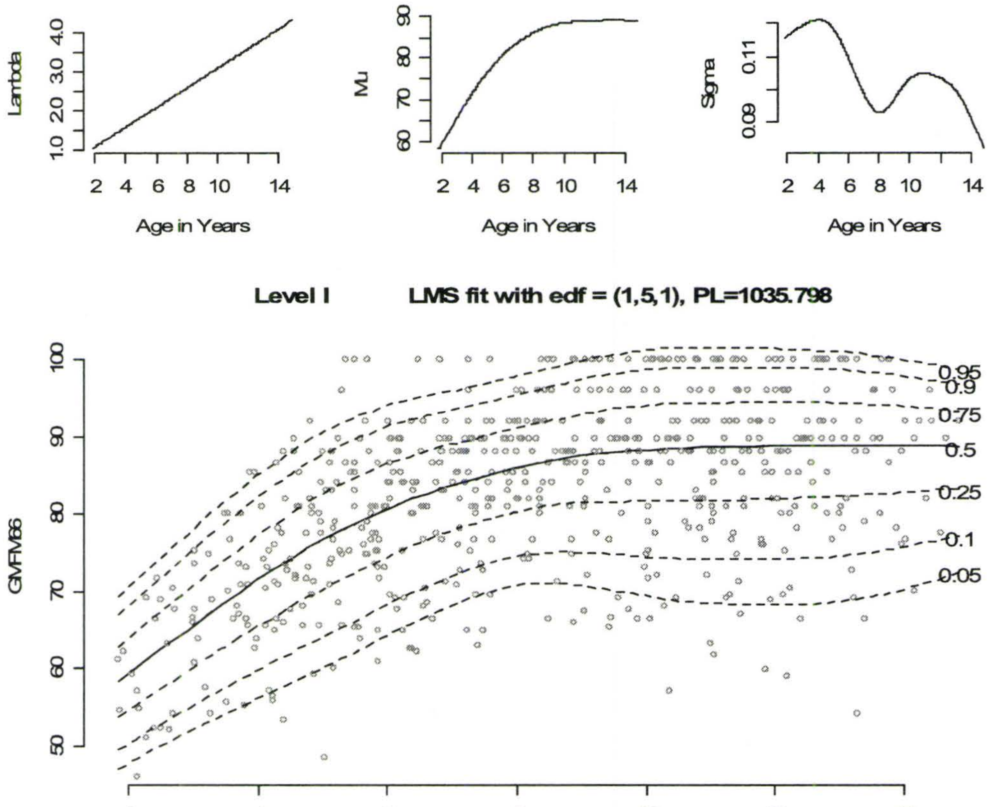

Figure 1: The fitted GMFM66 cross-sectional LMS regression centile curves and the smooth curves of *L*, *M* and *S* for Level I

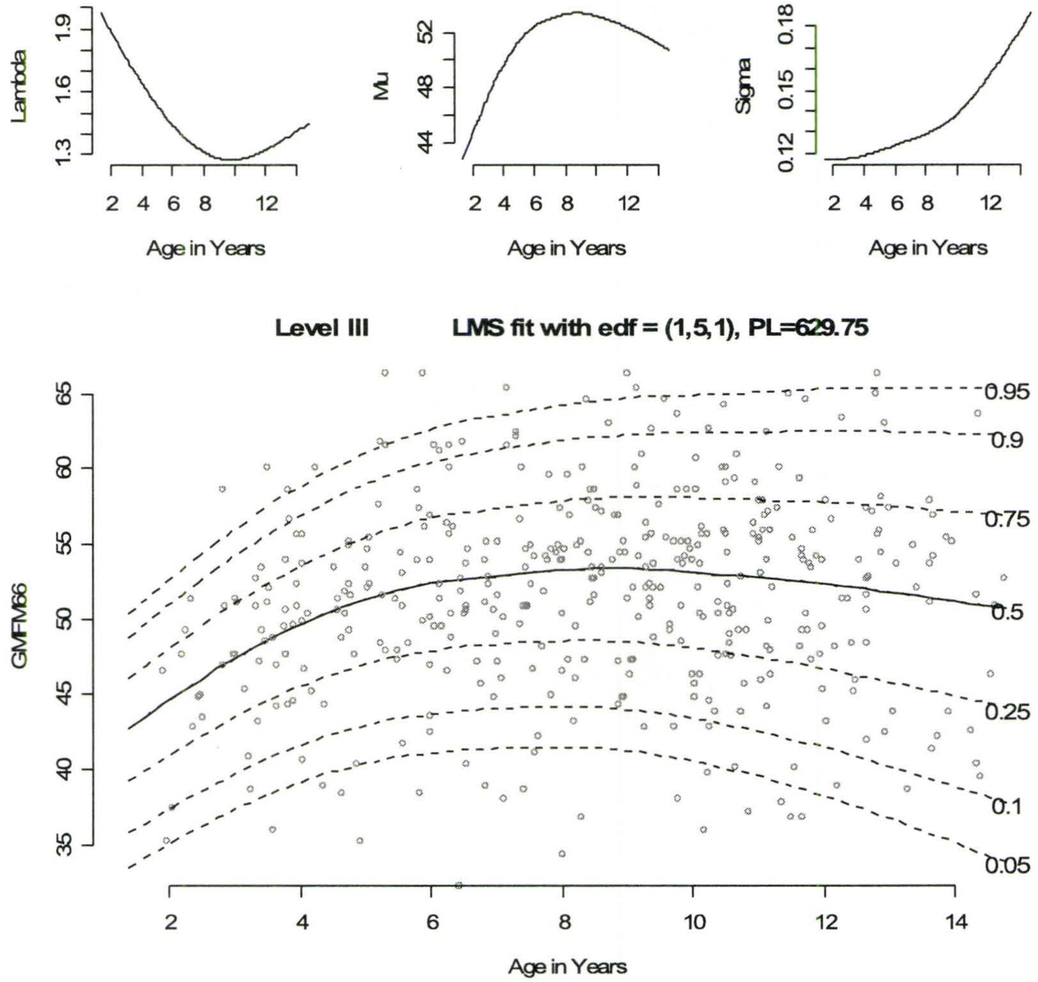

Figure 2: The fitted GMFM66 cross-sectional LMS regression centile curves and the smooth curves of L, M and S for Level III

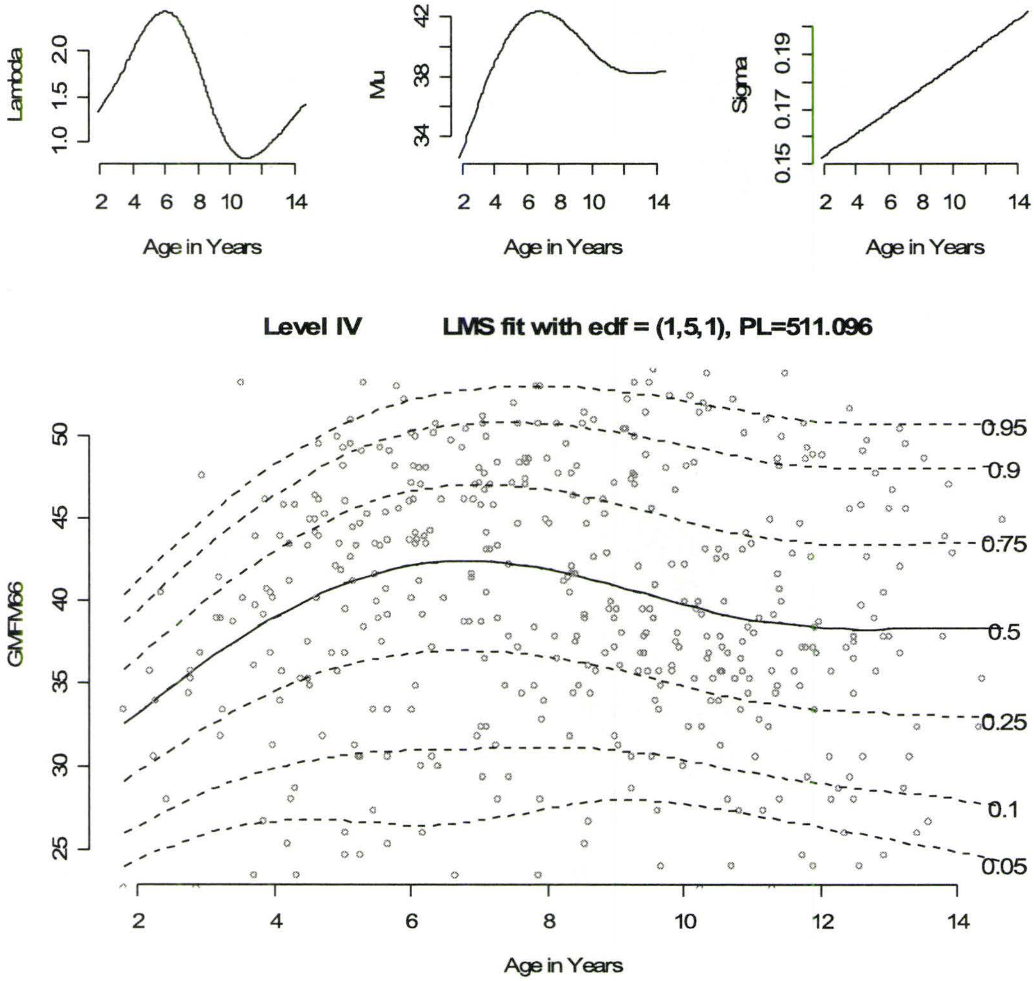

Figure 3: The fitted GMFM66 cross-sectional LMS regression centile curves and the smooth curves of L, M and S for Level IV

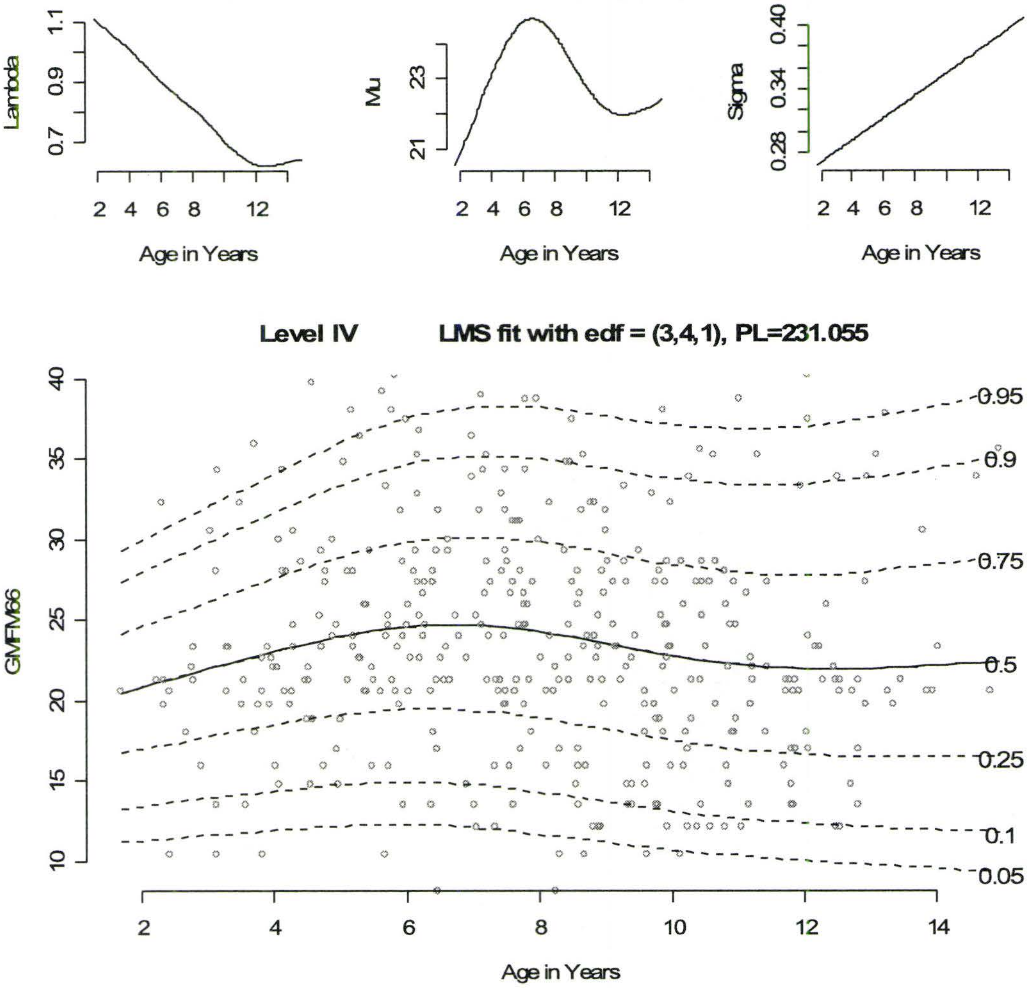

Figure 4: The fitted GMFM66 cross-sectional LMS regression centile curves and the smooth curves of L, M and S for Level V

APPENDIX B

CONDITIONAL LMS CENTILE CURVES

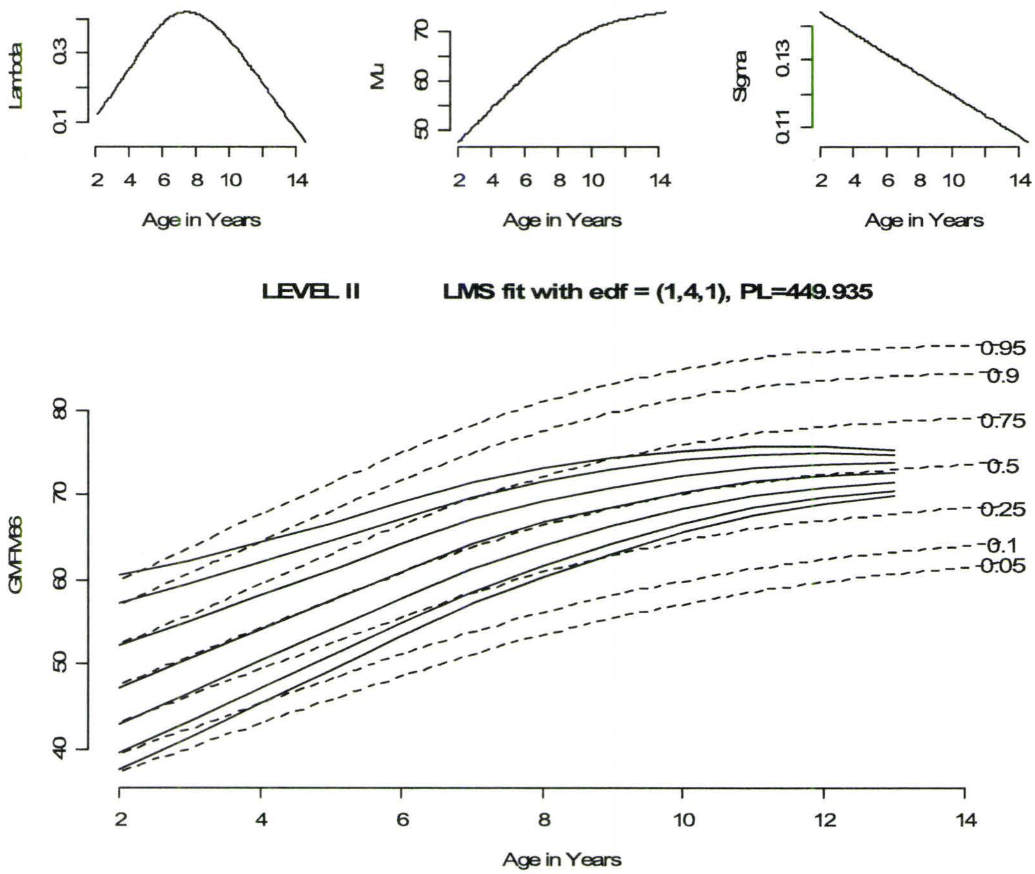

Figure 1: Cross-sectional LMS regression centile curves (dashed lines) vs. median GMFM66 conditional velocity centiles (solid lines) for Level II

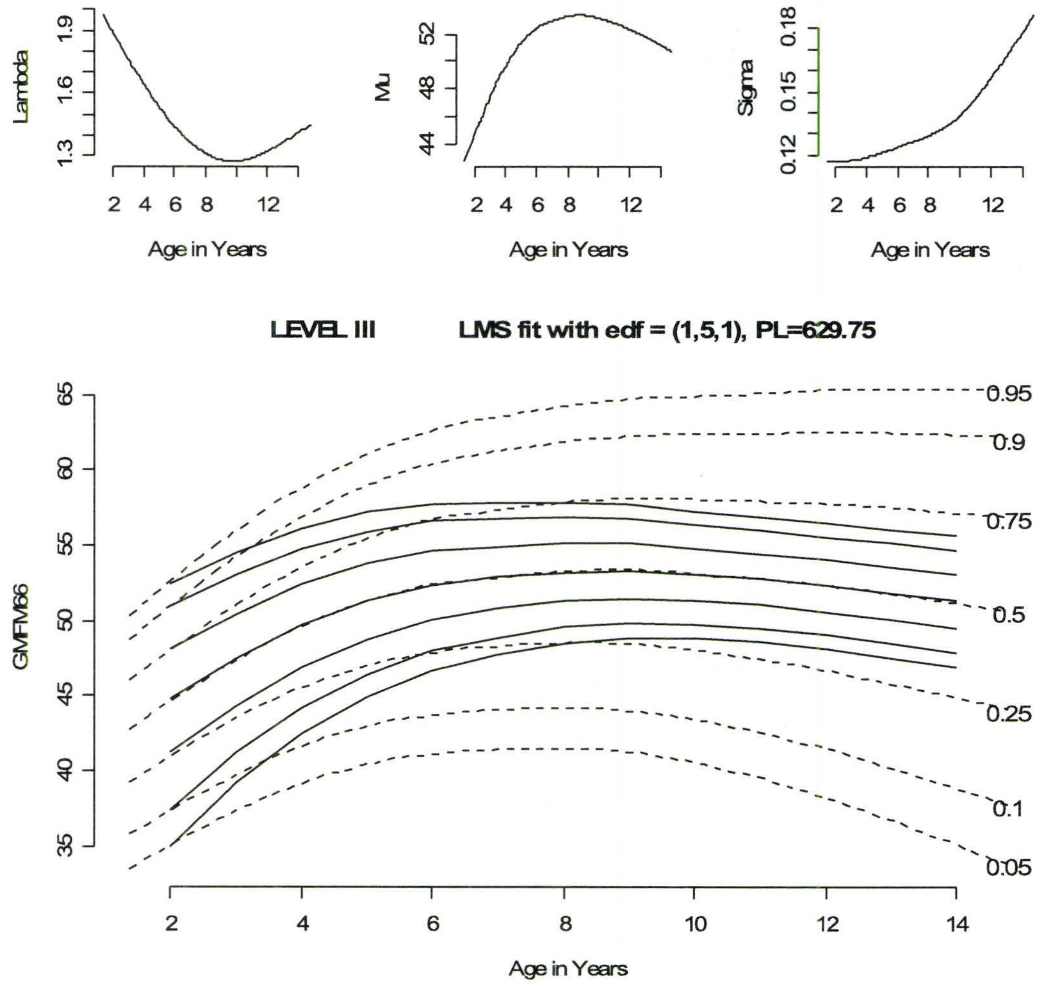

Figure 2: Cross-sectional LMS regression centile curves (dashed lines) vs. median GMFM66 conditional velocity centiles (solid lines) for Level III

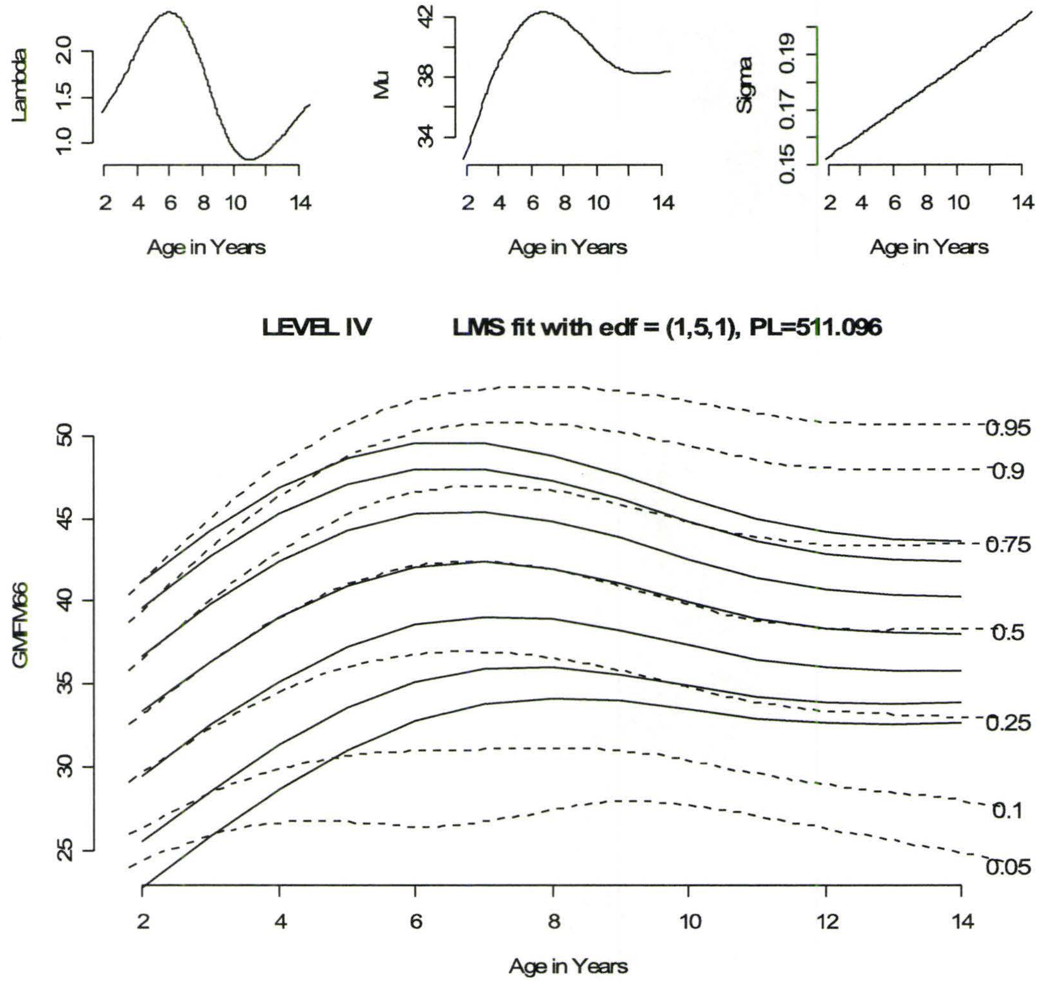

Figure 3: Cross-sectional LMS regression centile curves (dashed lines) vs. median GMFM66 conditional velocity centiles (solid lines) for Level IV

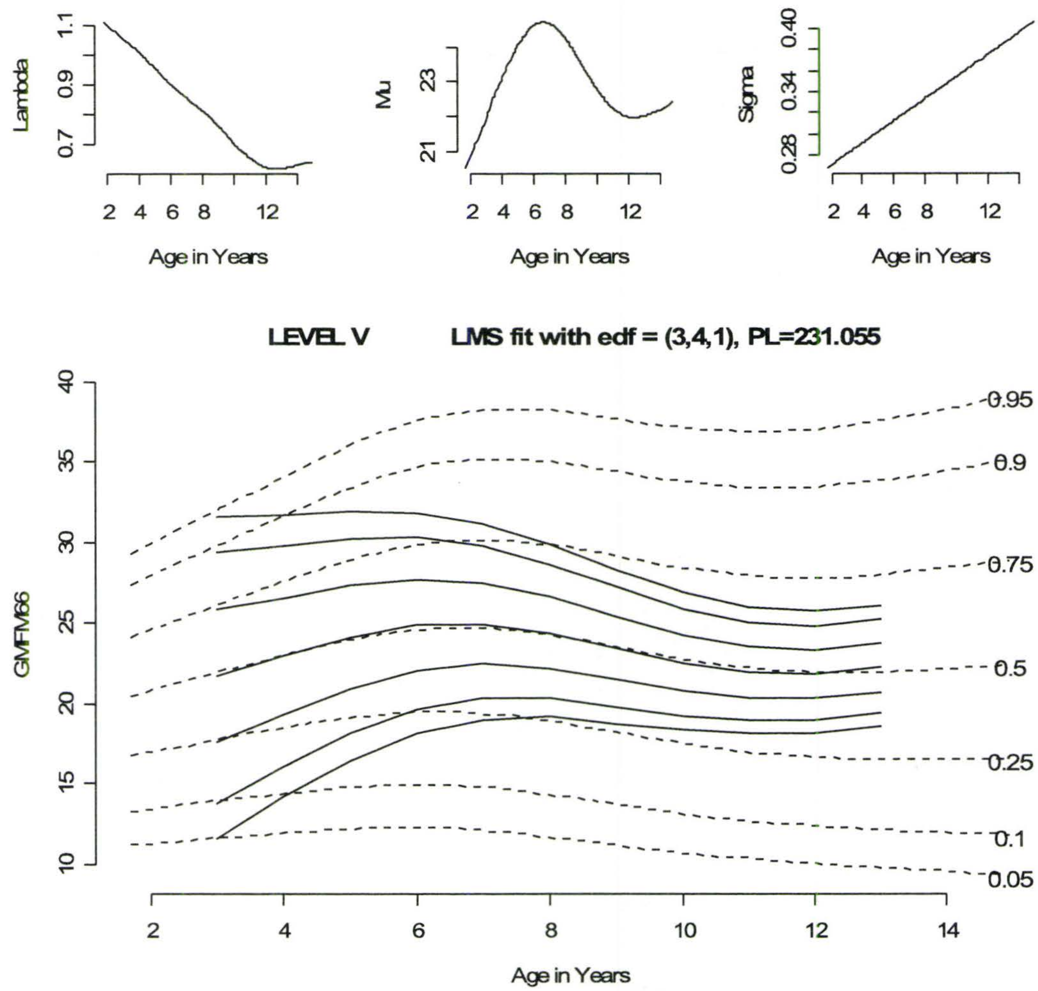

Figure 4: Cross-sectional LMS regression centile curves (dashed lines) vs. median GMFM66 conditional velocity centiles (solid lines) for Level V

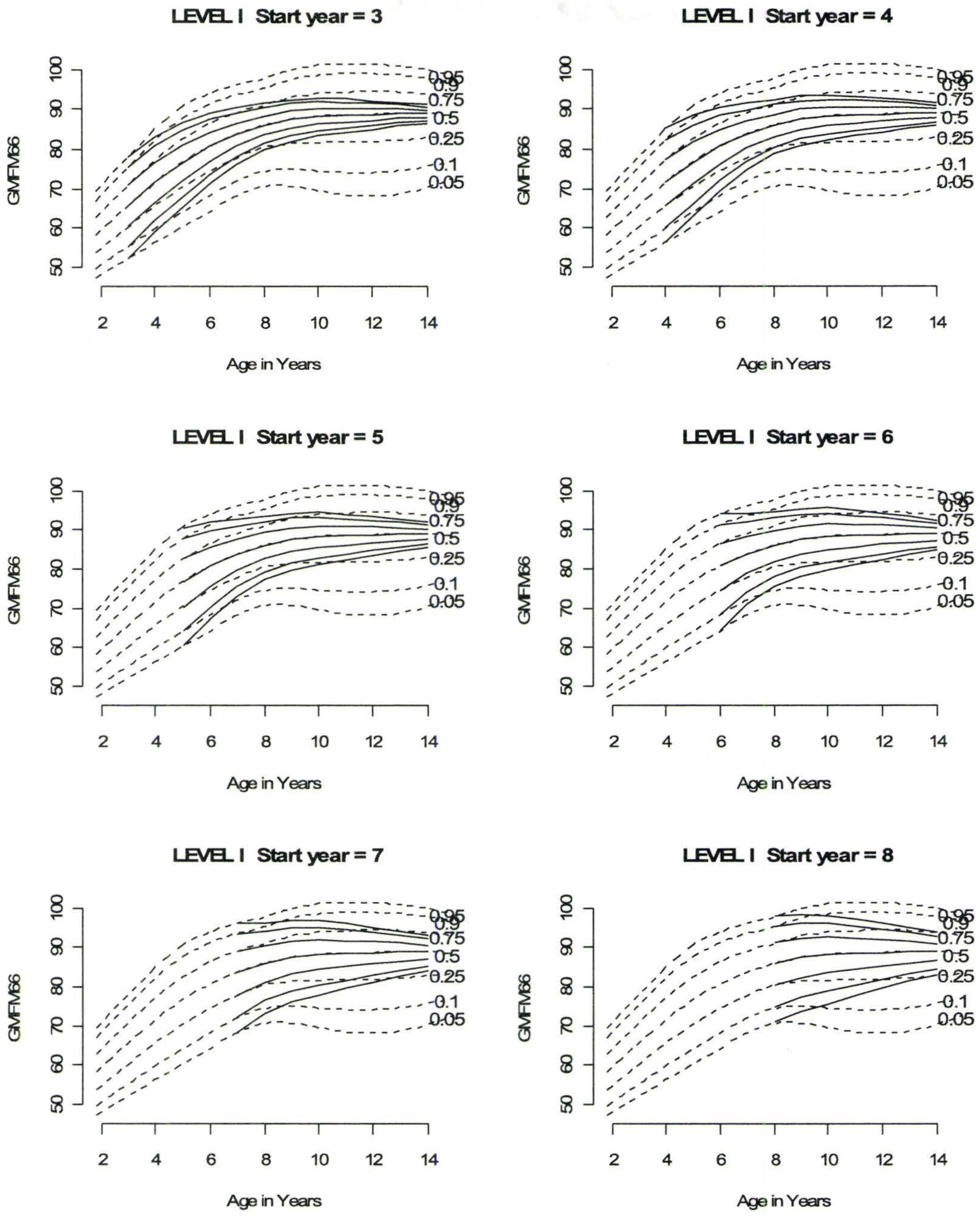

Figure 5 (a): Cross-sectional LMS centiles (dashed lines) vs. median GMFM conditional LMS centiles (solid lines) with different starting age for Level I

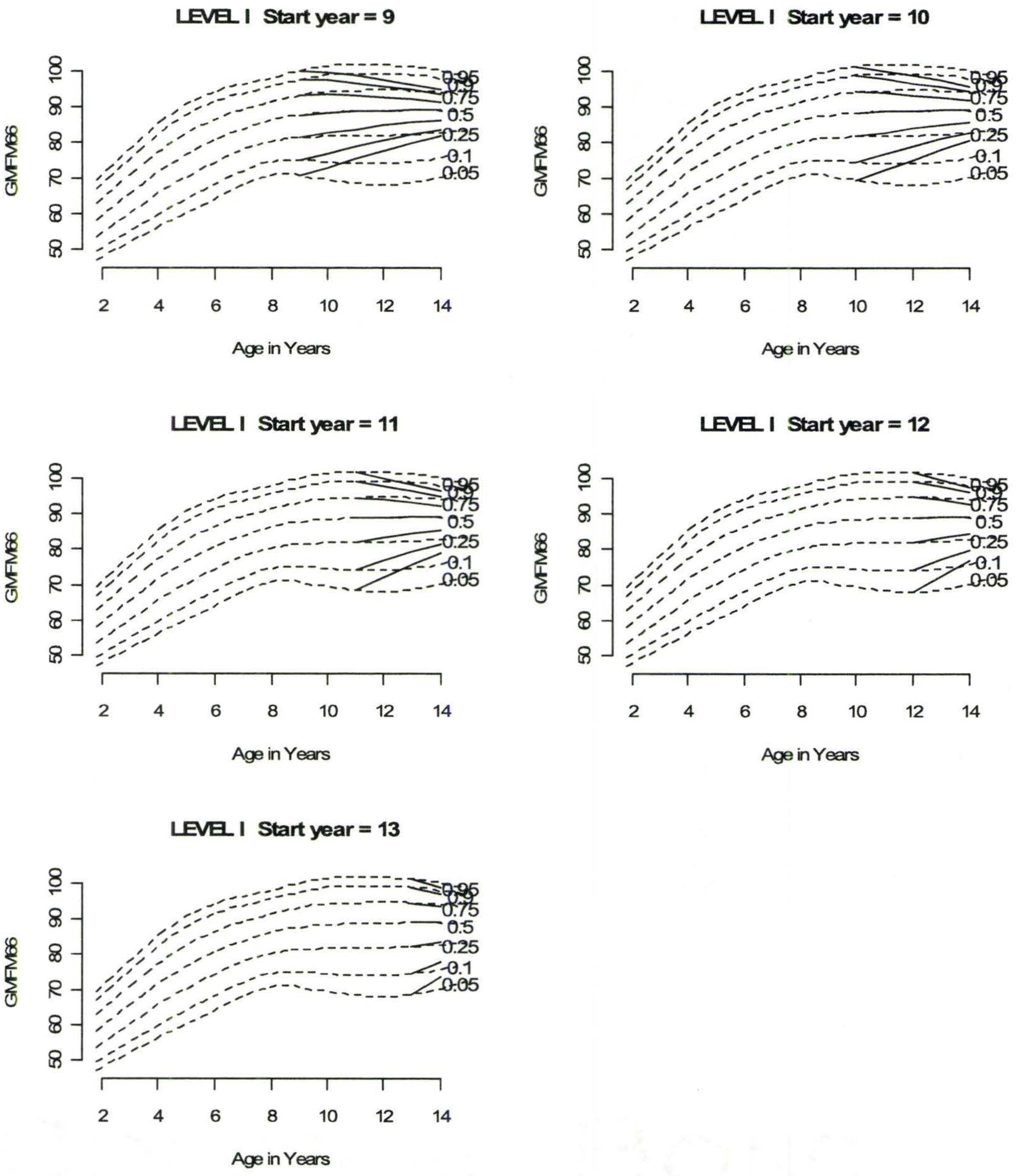

Figure 5 (b): Cross-sectional LMS centiles (dashed lines) vs. median GMFM conditional LMS centiles (solid lines) with different starting age for Level I

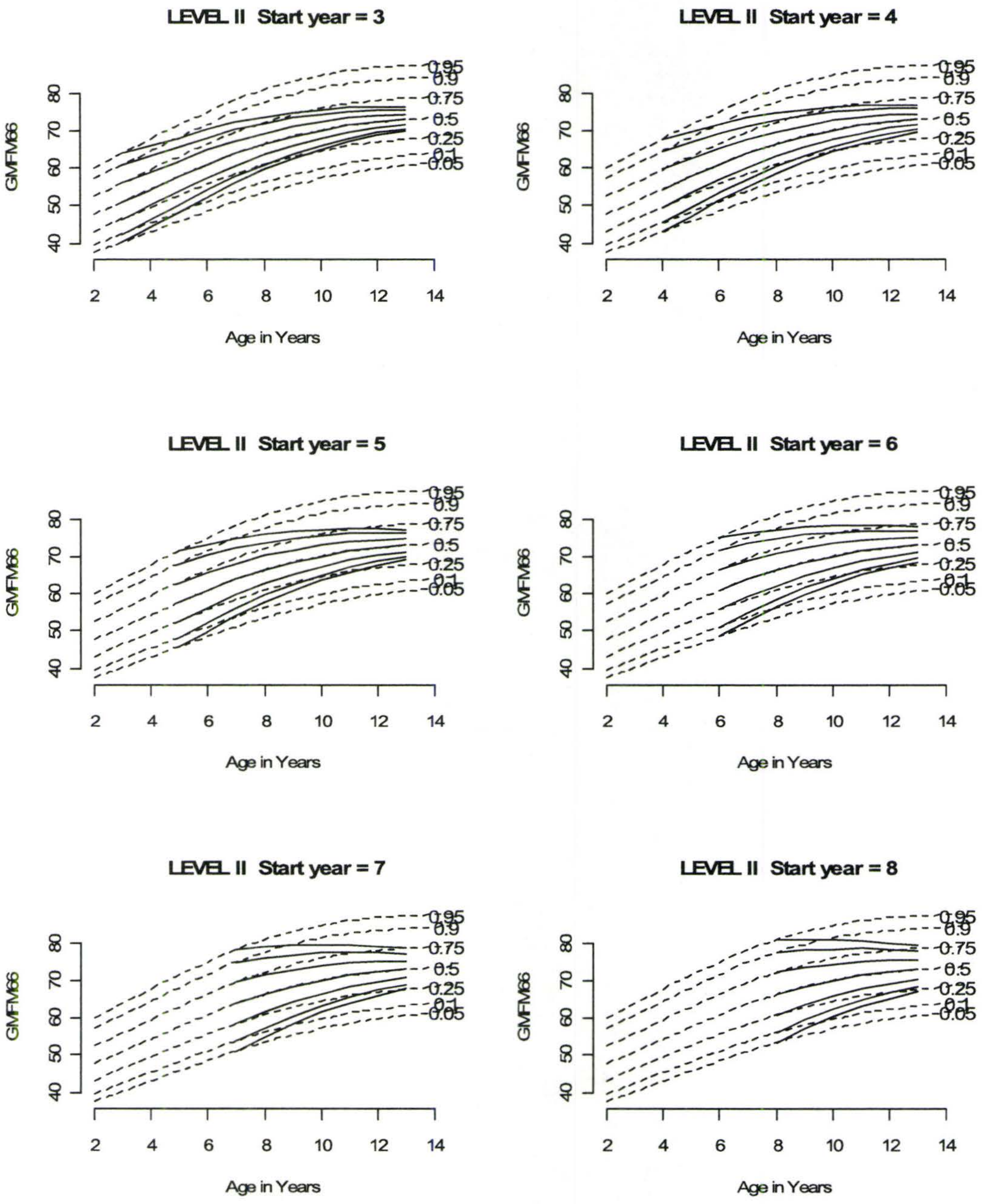

Figure 6 (a): Cross-sectional LMS centiles (dashed lines) vs. median GMFM conditional LMS centiles (solid lines) with different starting age for Level II

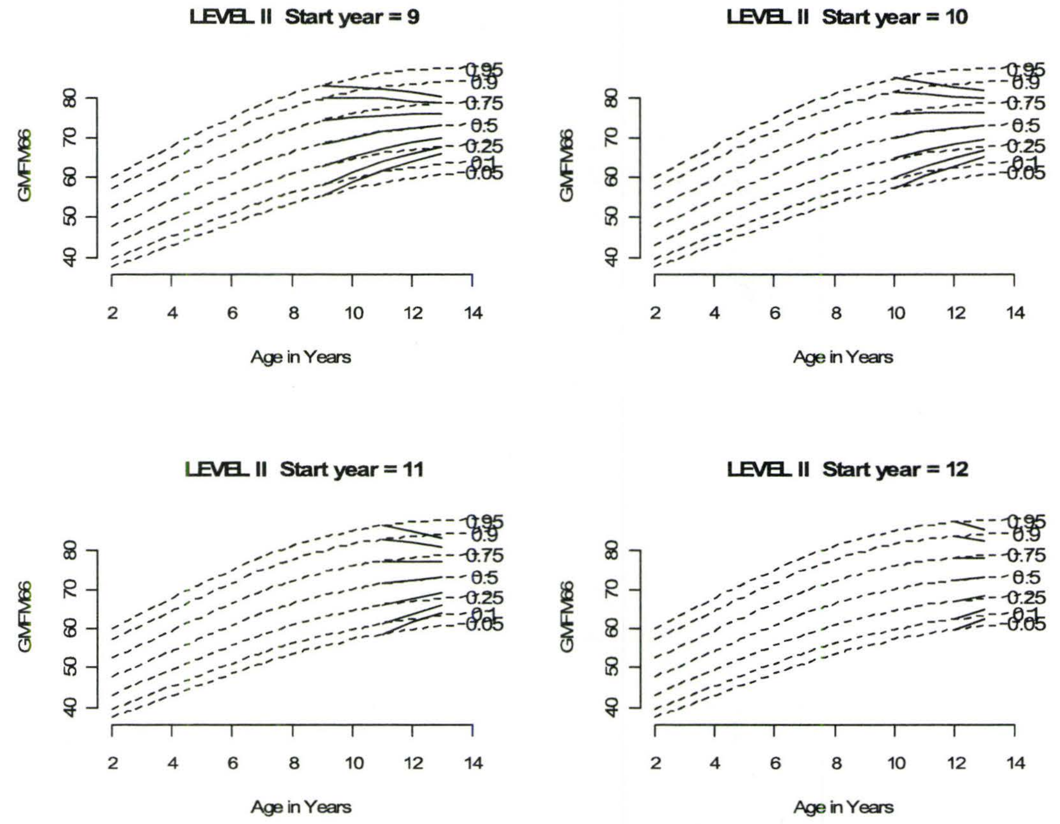

Figure 6 (b): Cross-sectional LMS centiles (dashed lines) vs. median GMFM conditional LMS centiles (solid lines) with different starting age for Level II

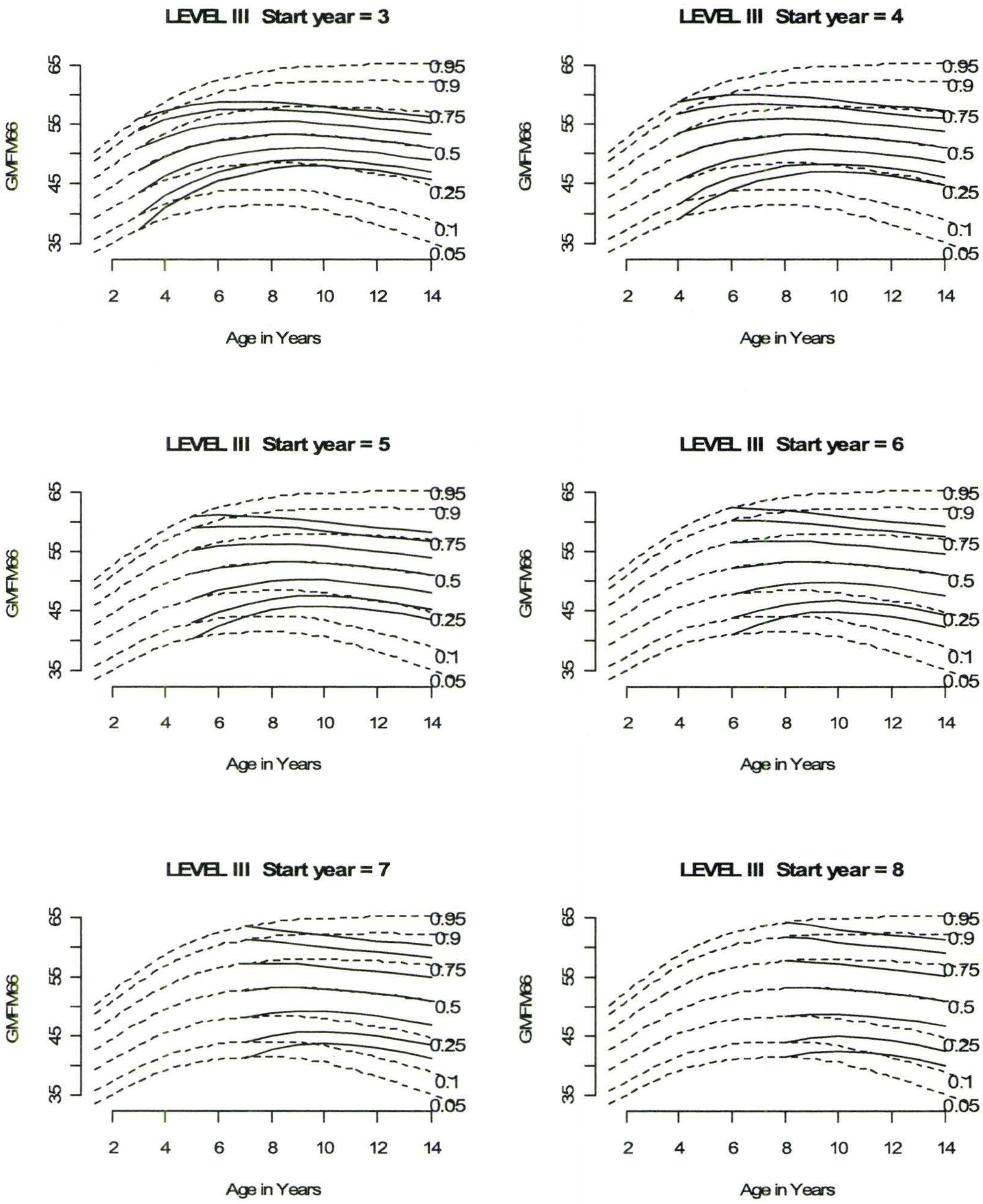

Figure 7 (a): Cross-sectional LMS centiles (dashed lines) vs. median GMFM conditional LMS centiles (solid lines) with different starting age for Level III

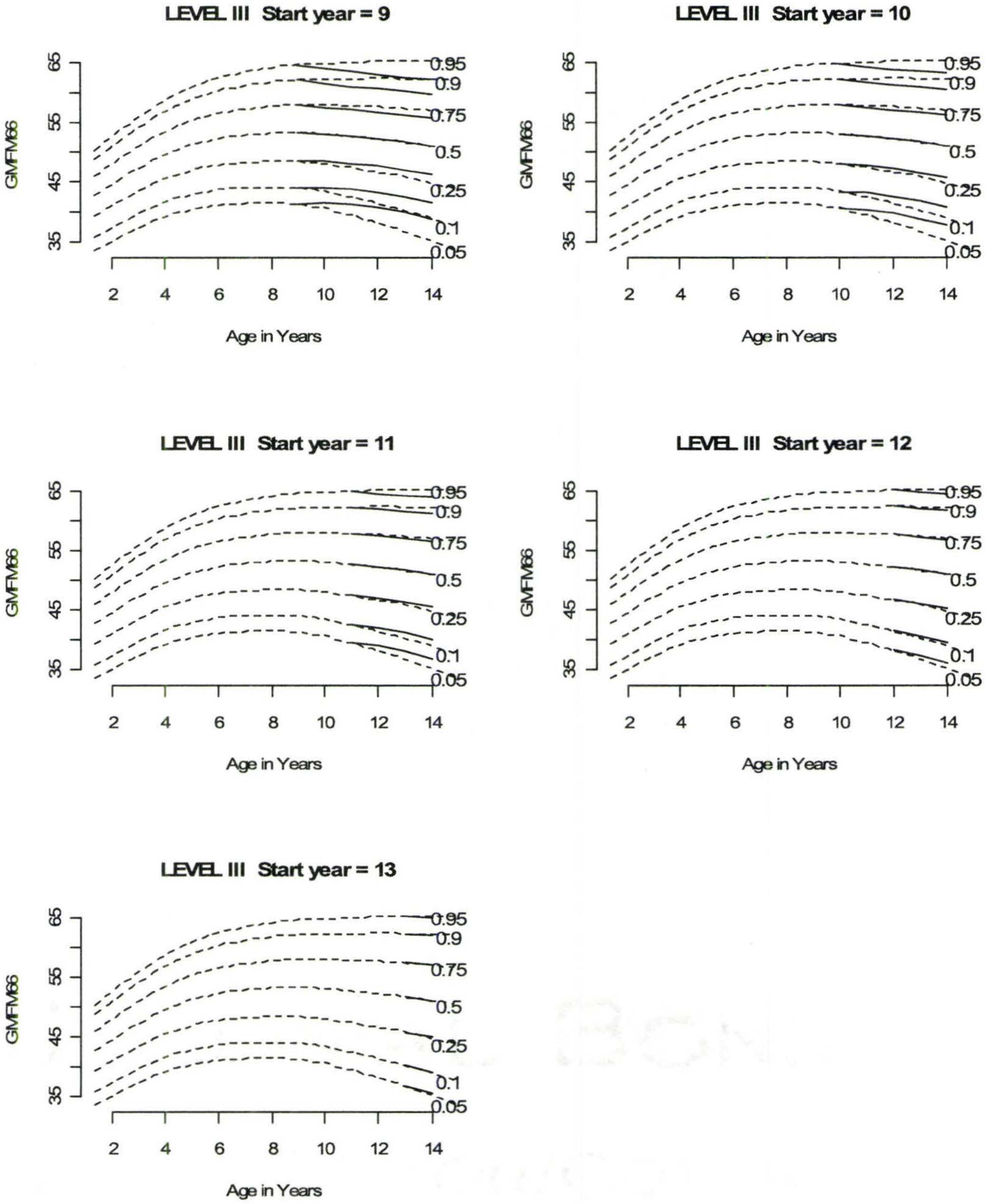

Figure 7 (b): Cross-sectional LMS centiles (dashed lines) vs. median GMFM conditional LMS centiles (solid lines) with different starting age for Level III

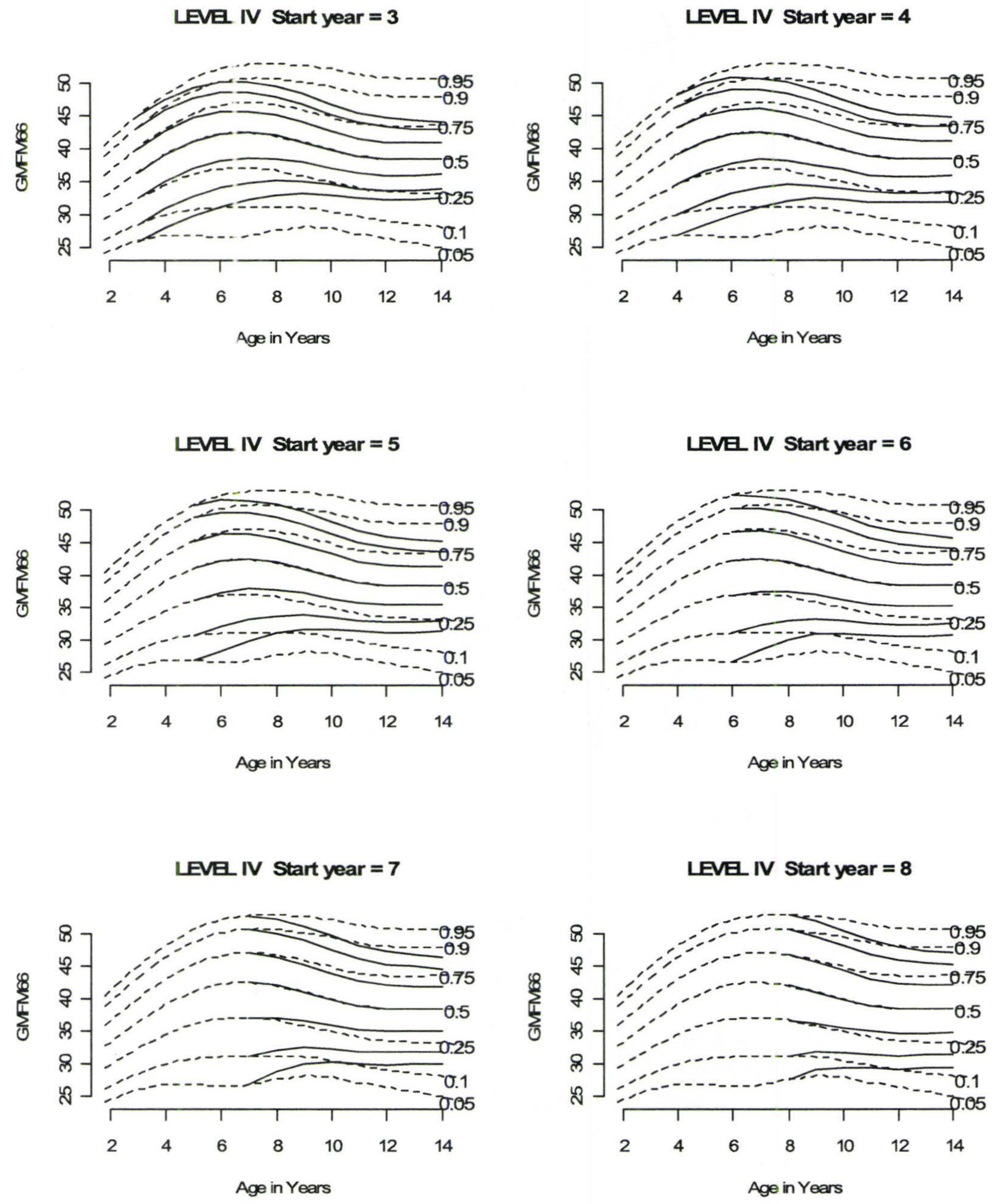

Figure 8 (a): Cross-sectional LMS centiles (dashed lines) vs. median GMFM conditional LMS centiles (solid lines) with different starting age for Level IV

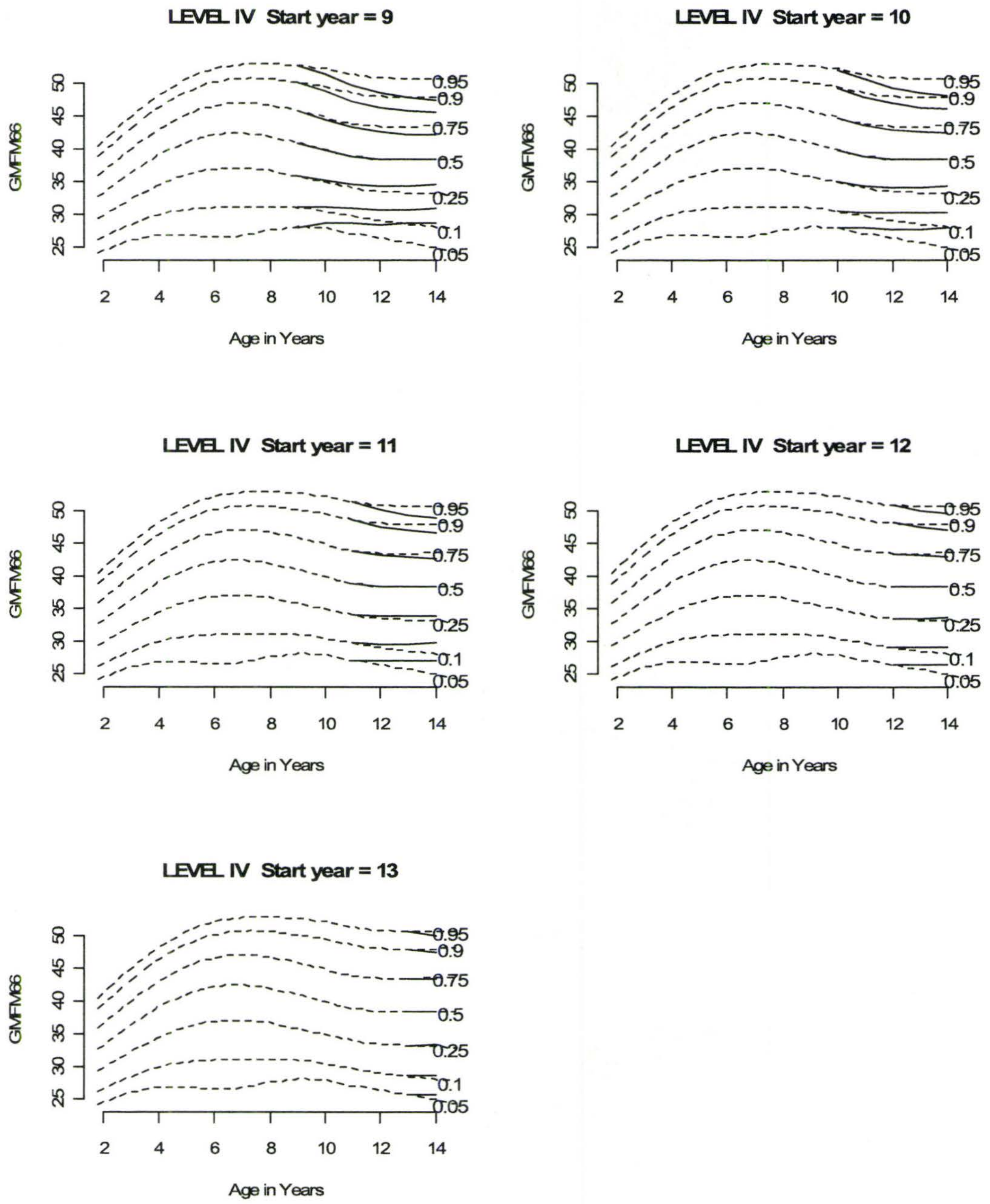

Figure 8 (b): Cross-sectional LMS centiles (dashed lines) vs. median GMFM conditional LMS centiles (solid lines) with different starting age for Level IV

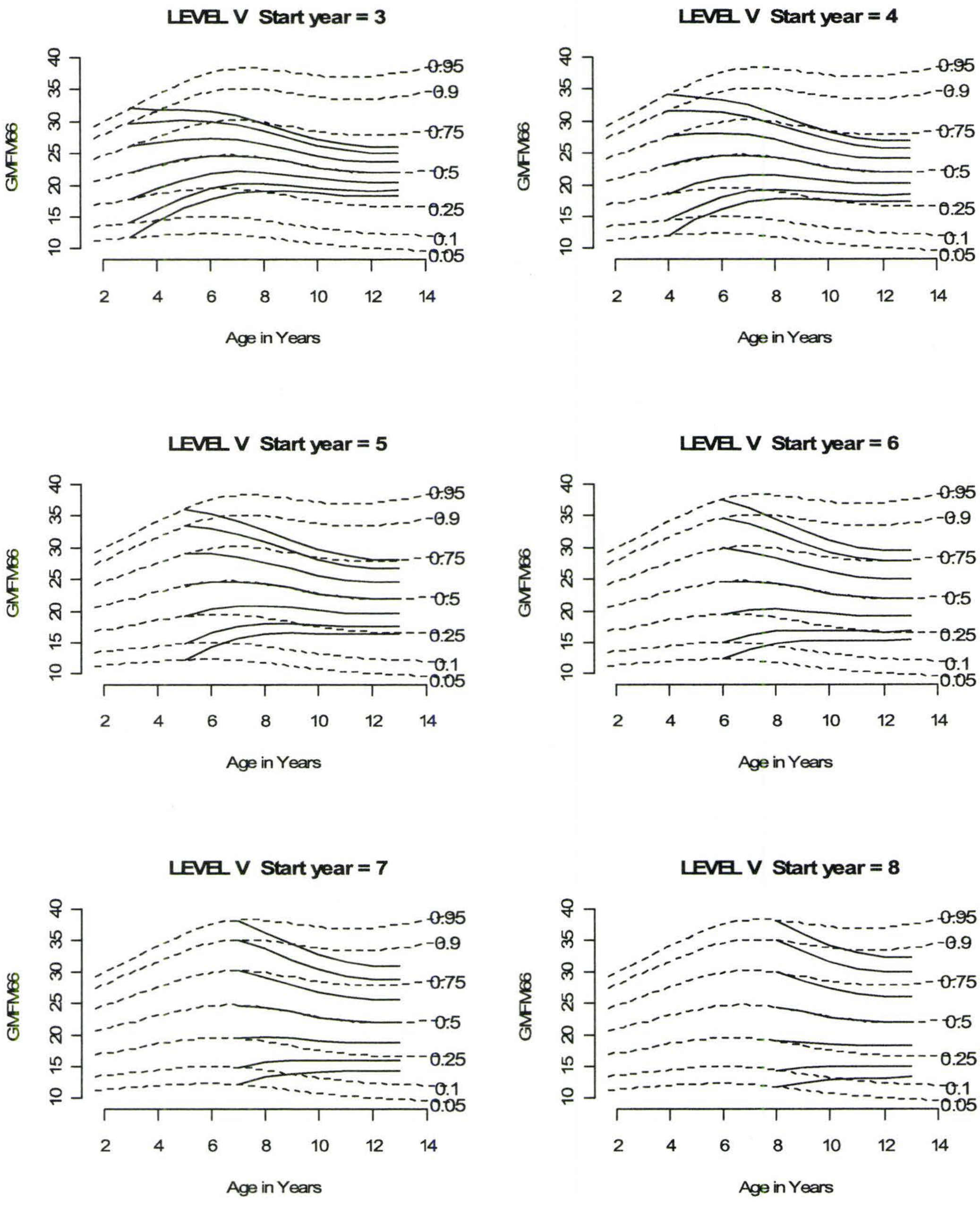

Figure 9 (a): Cross-sectional LMS centiles (dashed lines) vs. median GMFM conditional LMS centiles (solid lines) with different starting age for Level V

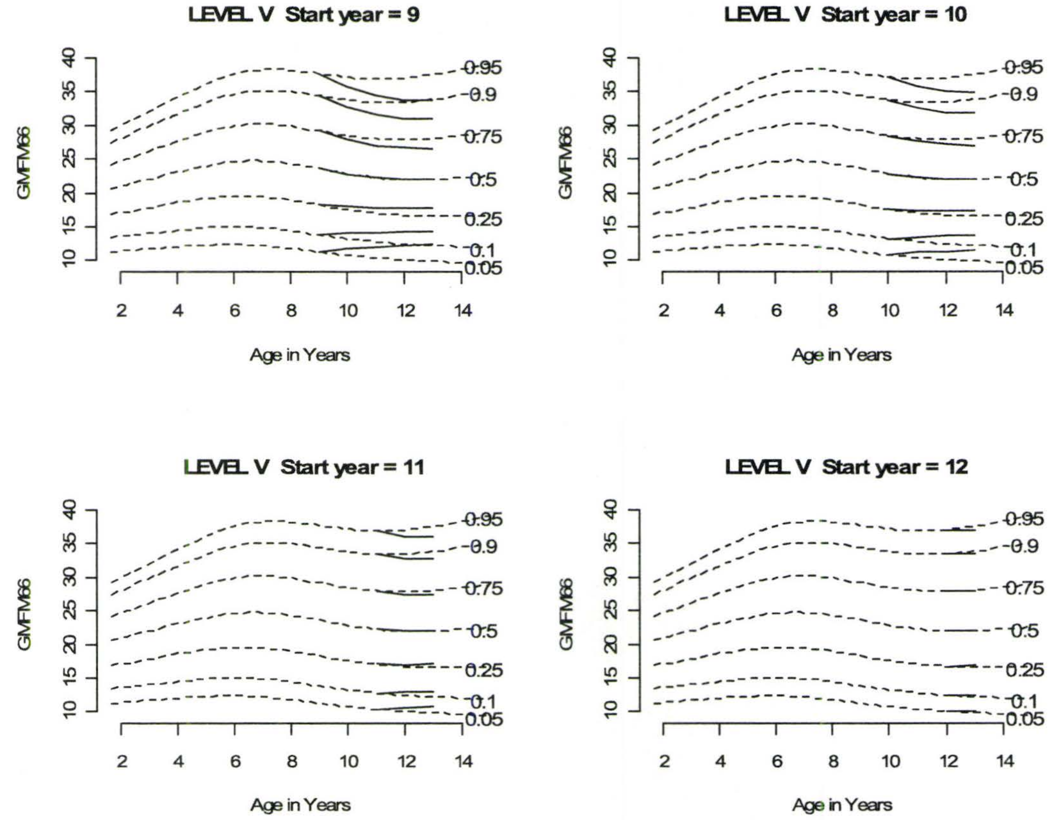

Figure 9 (b): Cross-sectional LMS centiles (dashed lines) vs. median GMFM conditional LMS centiles (solid lines) with different starting age for Level V

APPENDIX C

CONDITIONAL CENTILES FOR PARTICULAR PATIENT

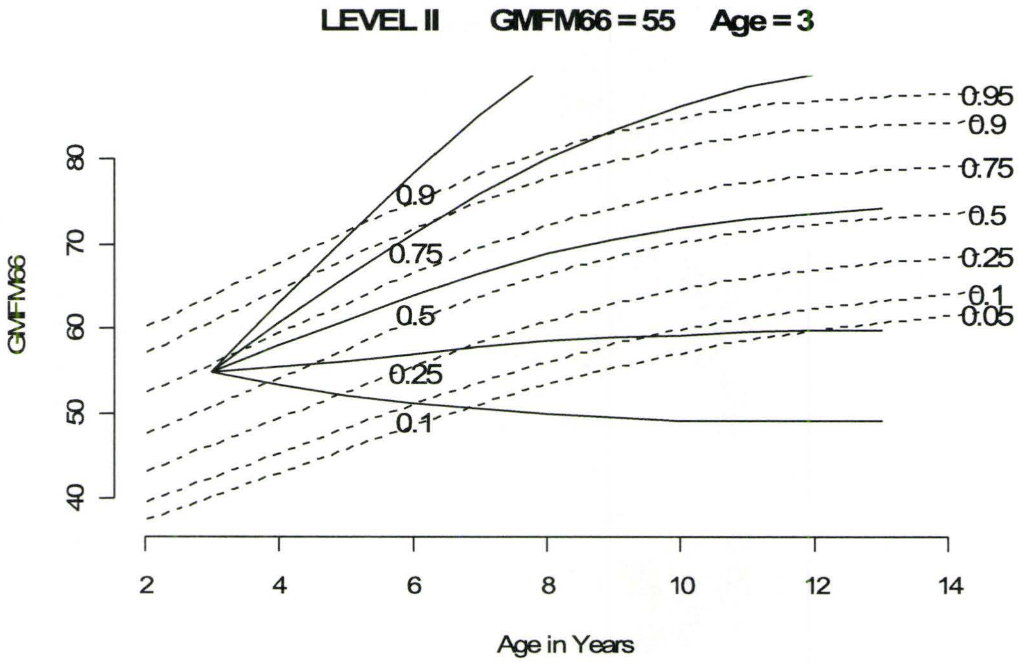

Figure 1: Cross-sectional LMS regression centile curves (dashed lines) vs. conditional velocity centiles (solid lines) for a child starting at age 3 and GMFM66 55 in Level II

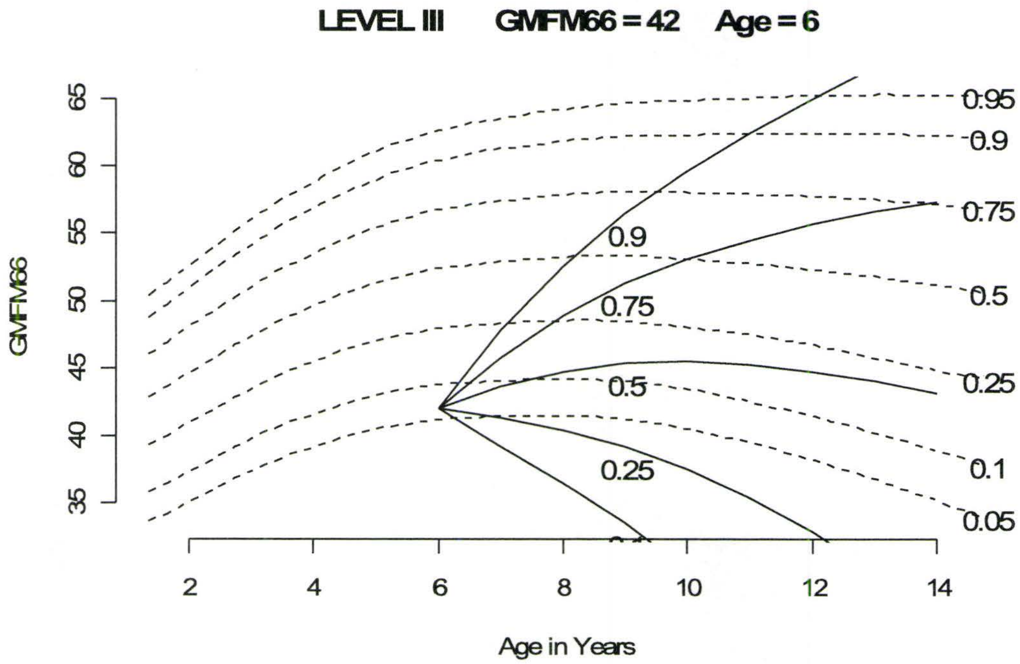

Figure 2: Cross-sectional LMS regression centile curves (dashed lines) vs. conditional velocity centiles (solid lines) for a child starting at age 6 and GMFM66 42 in Level III

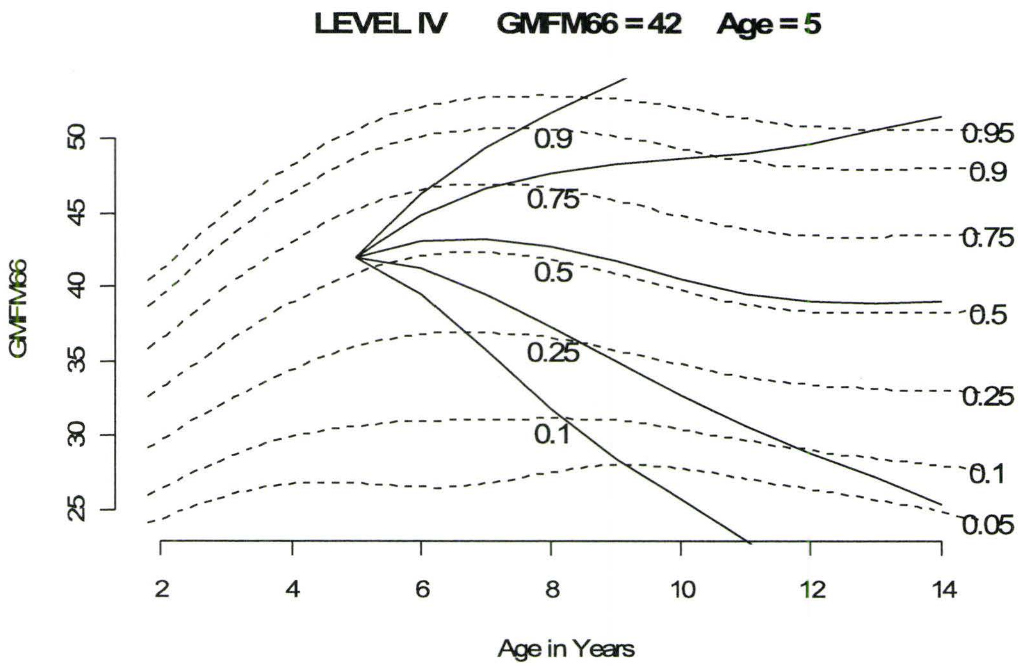

Figure 3: Cross-sectional LMS regression centile curves (dashed lines) vs. conditional velocity centiles (solid lines) for a child starting at age 5 and GMFM66 42 in Level IV

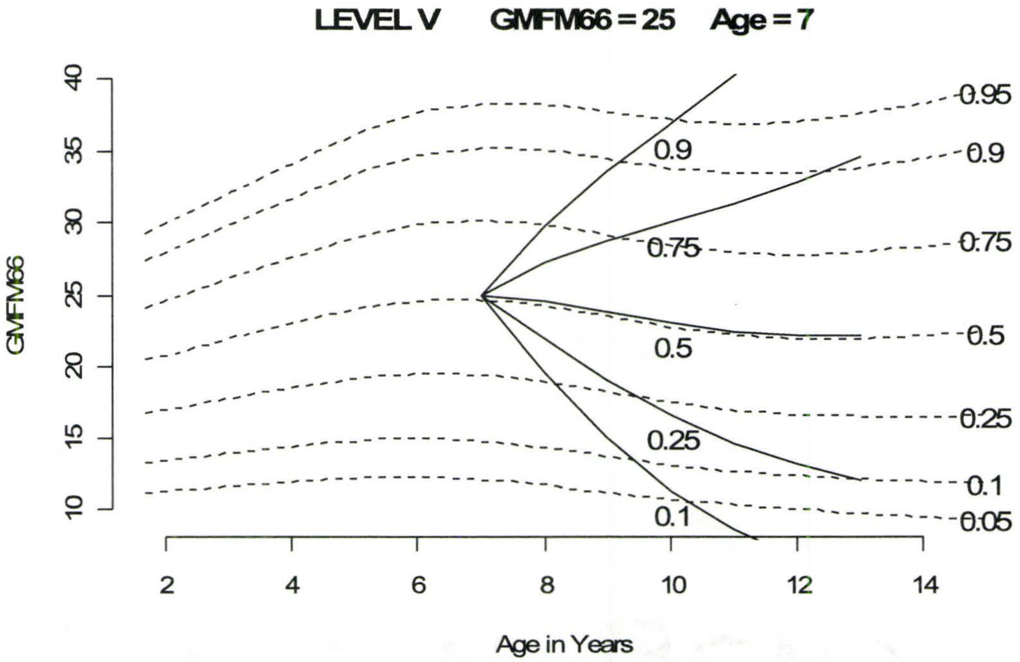

Figure 4: Cross-sectional LMS regression centile curves (dashed lines) vs. conditional velocity centiles (solid lines) for a child starting at age 7 and GMFM66 25 in Level V

APPENDIX D

ADDITIONAL PLOTS AND TABELS FOR LEVEL I - V

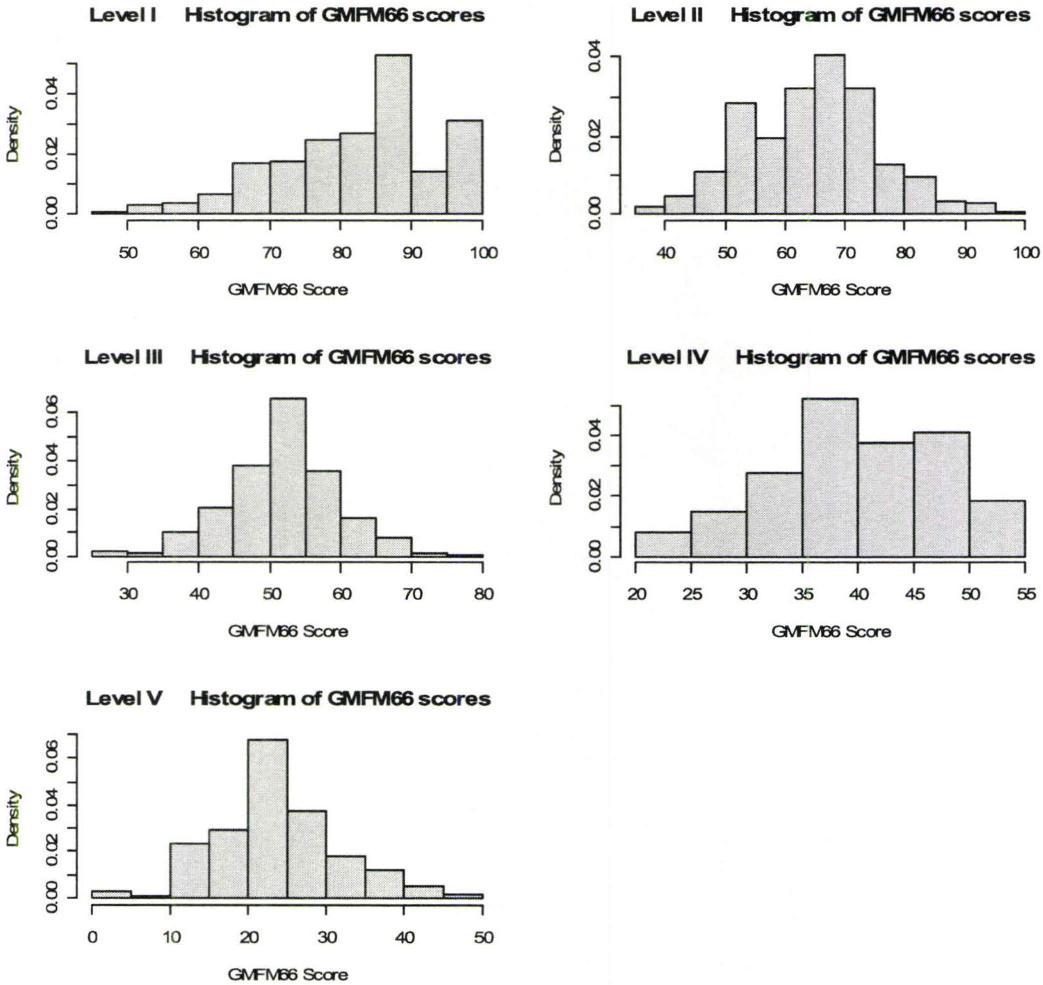

Figure 1: Histogram of GMFM66 scores for Level I to V

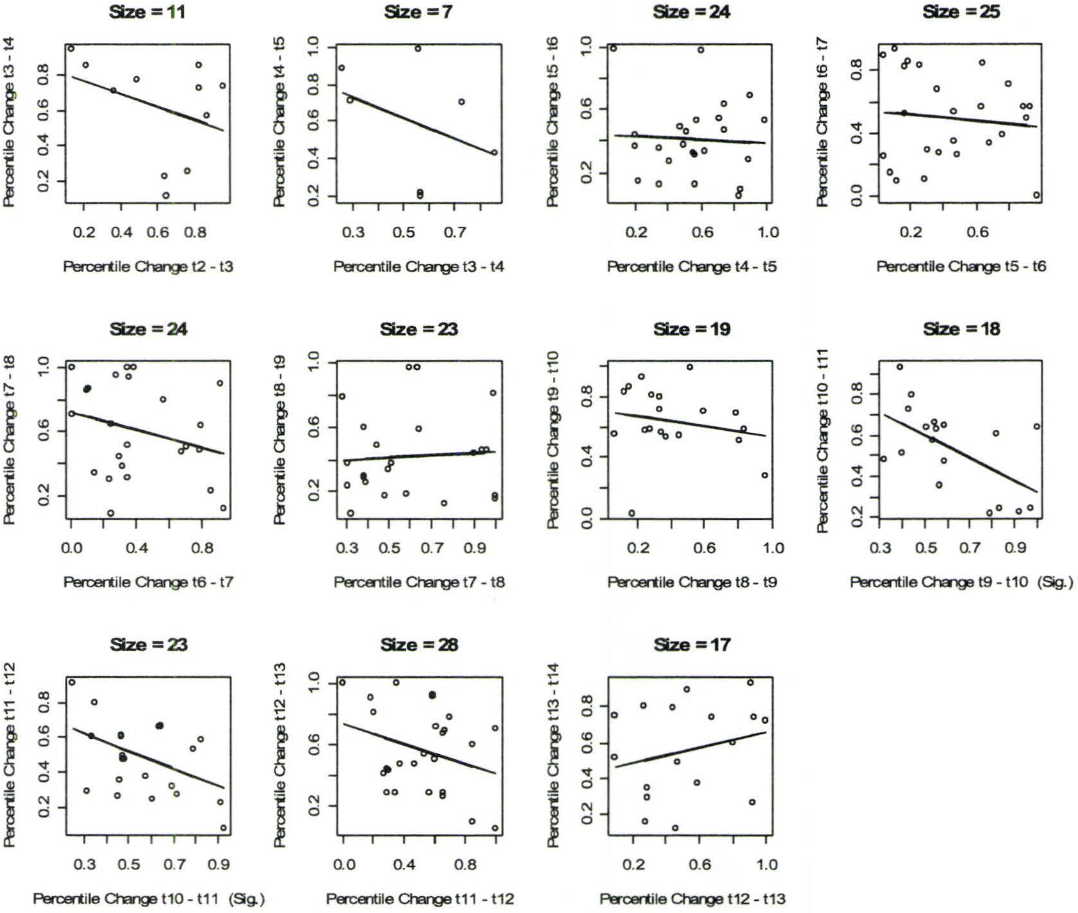

Figure 2: Percentage changes in Level I. (The solid line in each plot is the regression line, and the significant regression is specified by (Sig) in the label of the x-axis)

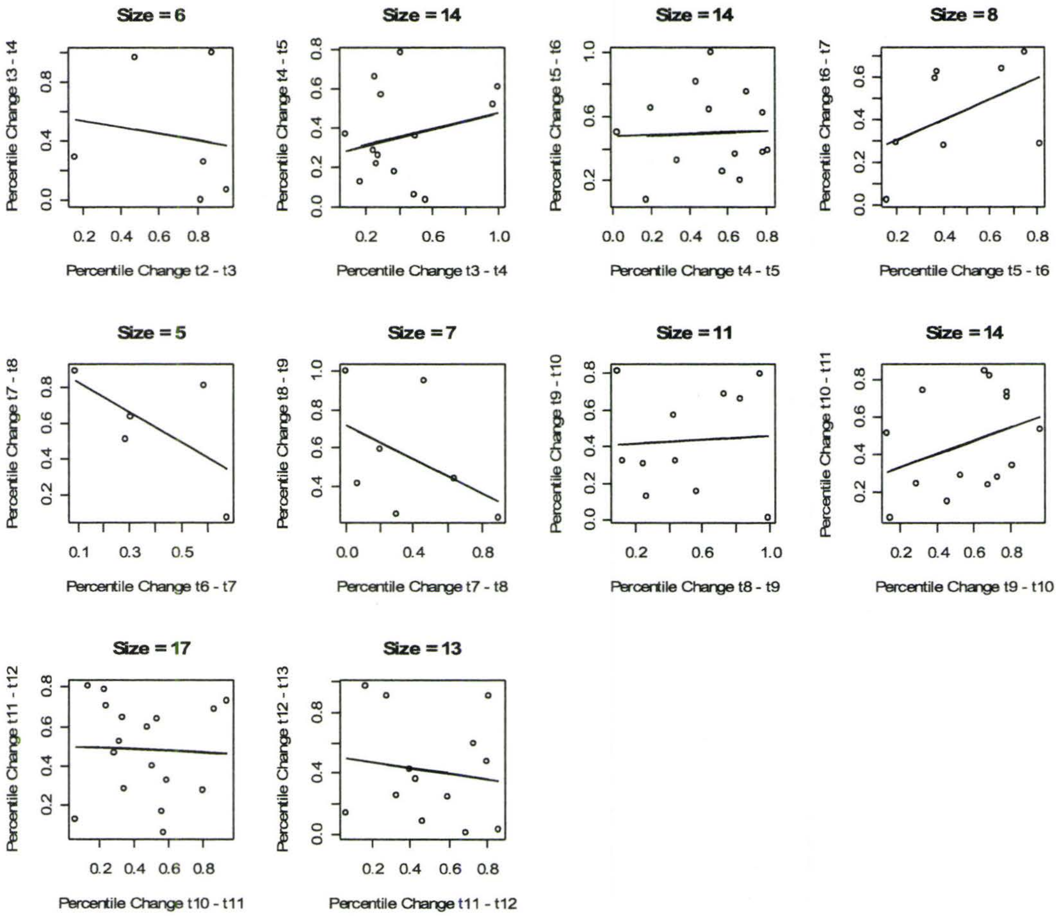

Figure 3: Percentage changes in Level II. (The solid line in each plot is the regression line, and the significant regression is specified by (Sig) in the label of the x-axis)

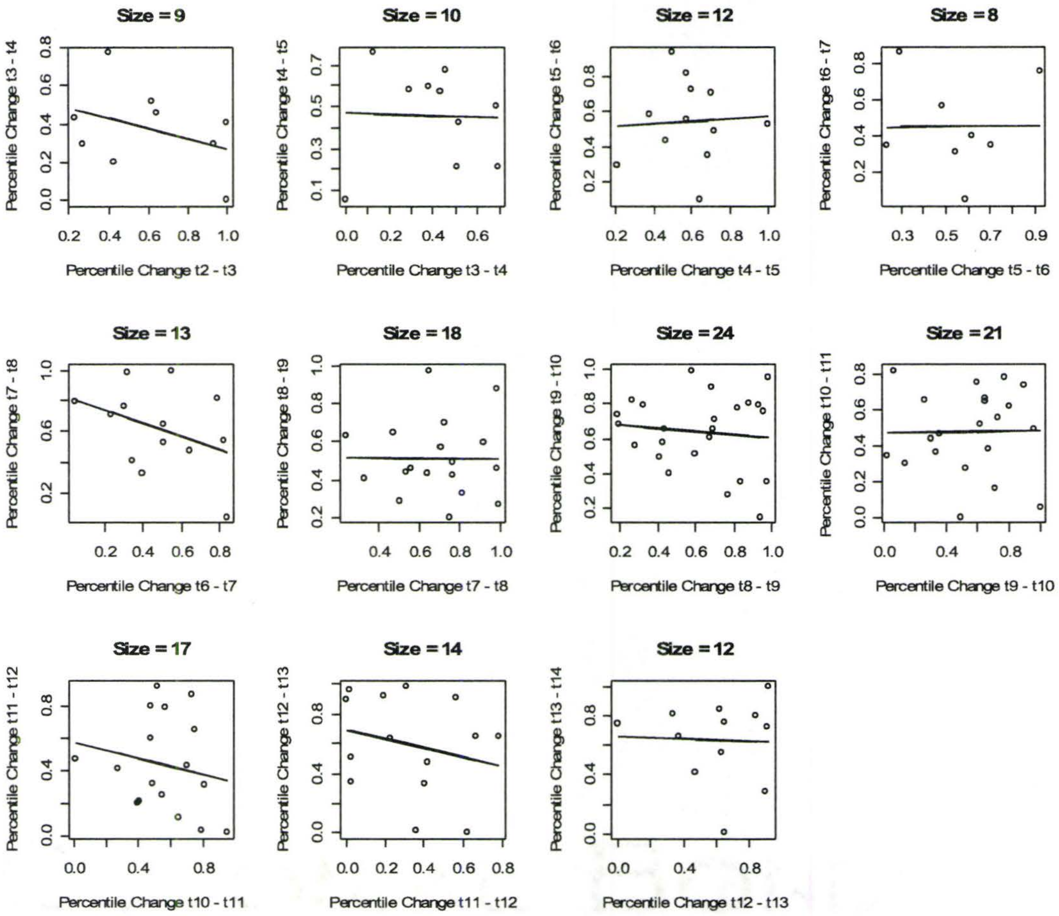

Figure 4: Percentage changes in Level III. (The solid line in each plot is the regression line, and the significant regression is specified by (Sig) in the label of the x-axis)

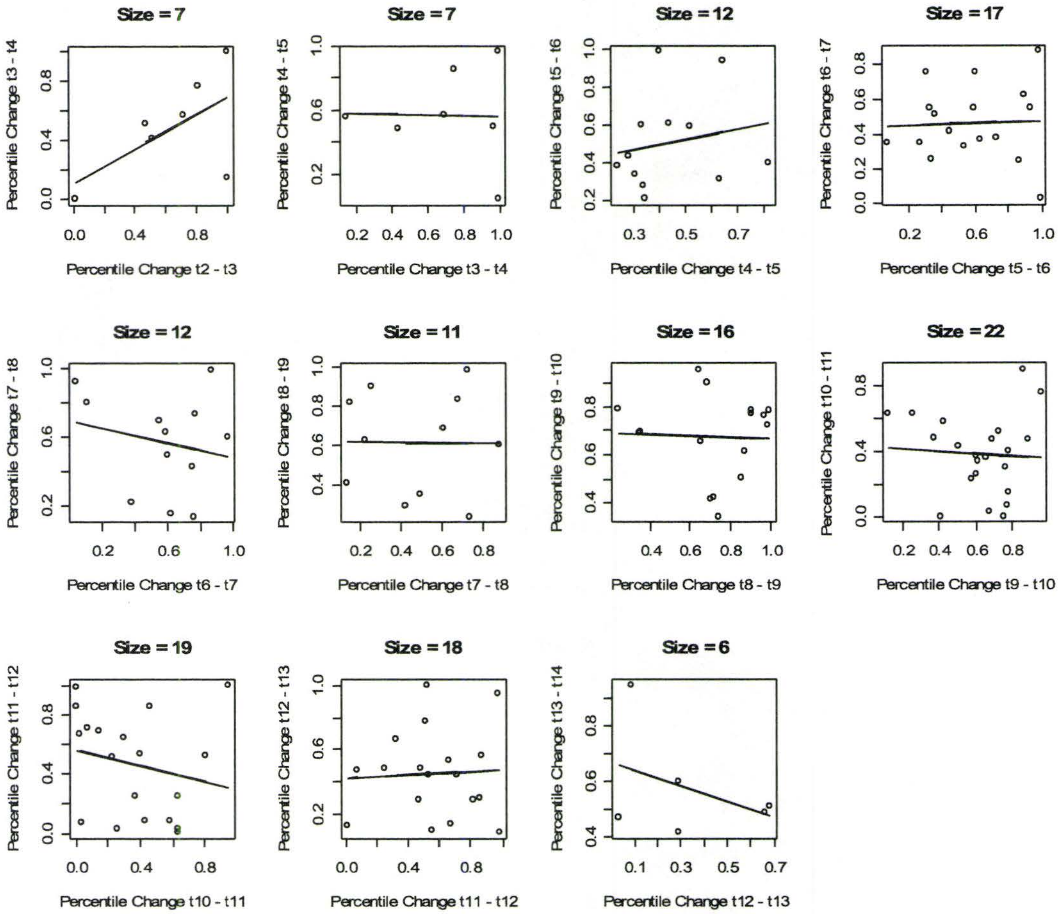

Figure 5: Percentage changes in Level IV. (The solid line in each plot is the regression line, and the significant regression is specified by (Sig) in the label of the x-axis)

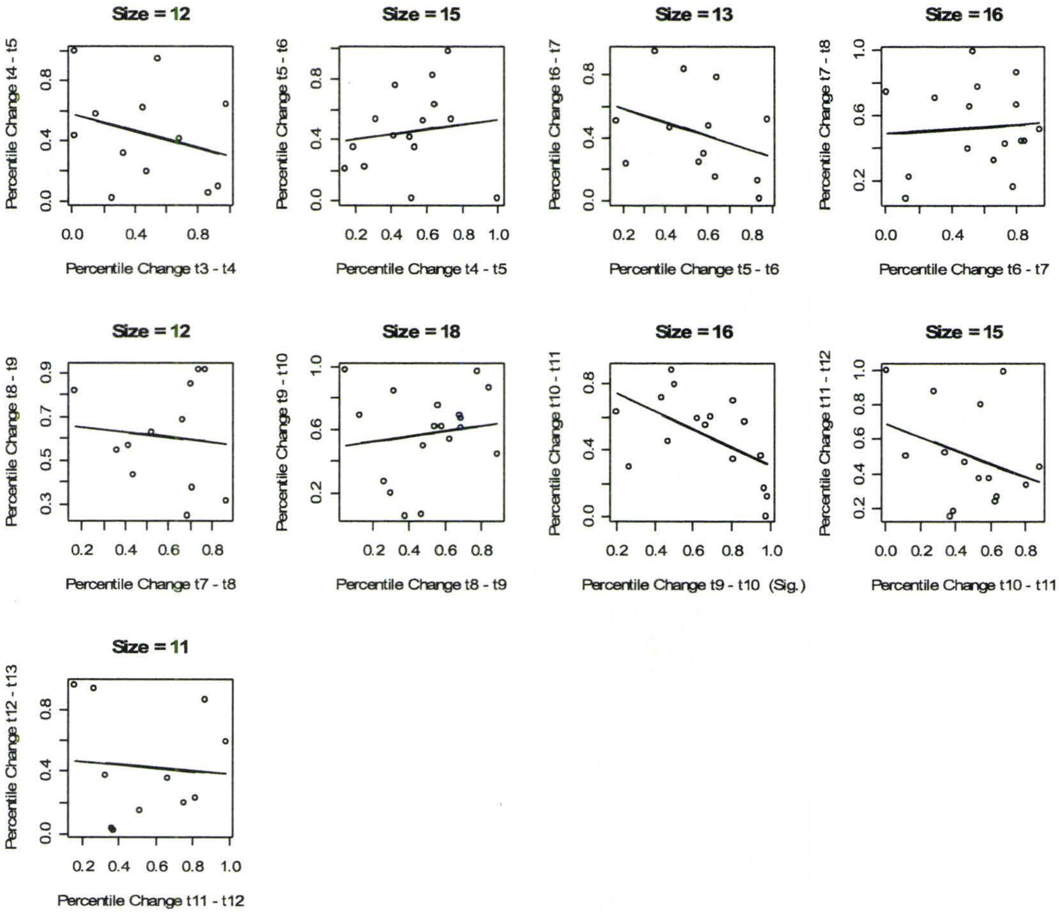

Figure 6: Percentage changes in Level V. (The solid line in each plot is the regression line, and the significant regression is specified by (Sig) in the label of the x-axis)

Level	Age	N	Mean(y-yhat)	SD(y-yhat)	Coverage
I	3	12	-0.0095	4.0079	1.0000
I	4	16	-0.0454	4.3974	0.9375
I	5	30	0.4530	5.2761	0.9000
I	6	48	-1.2137	5.3699	0.8750
I	7	42	-1.2978	4.6654	0.9524
I	8	39	1.6296	4.7576	0.8974
I	9	35	-0.5729	3.8751	1.0000
I	10	32	1.5887	4.5193	0.9375
I	11	36	0.7035	3.1195	1.0000
I	12	43	0.4337	5.9850	0.9302
I	13	36	1.0731	4.6723	0.9444
I	14	20	0.2571	3.2942	1.0000
Level I		**389**	**0.211**	**4.745**	**0.941**
II	3	6	1.6572	3.2367	1.0000
II	4	18	-0.6422	5.1055	0.8889
II	5	25	-1.3084	2.3256	1.0000
II	6	19	0.0359	3.8943	0.9474
II	7	15	-0.9720	2.9629	0.9333
II	8	11	0.0546	6.2416	0.8182
II	9	14	0.3451	5.3552	0.9286
II	10	23	0.5845	4.2803	0.9130
II	11	23	0.3959	3.4604	1.0000
II	12	21	0.4015	3.0569	1.0000
II	13	14	-1.0967	5.4487	0.9286
Level II		**189**	**0.144**	**4.082**	**0.947**
III	3	10	1.6944	4.4698	0.8000
III	4	17	-2.1522	3.4480	0.8824
III	5	19	0.4401	3.2565	0.9474
III	6	23	0.6476	2.5621	0.9565
III	7	18	0.0565	2.3793	1.0000
III	8	27	1.7552	3.2235	0.8519
III	9	34	1.0993	2.5569	0.9118
III	10	32	0.6277	2.4991	0.9688
III	11	33	0.2246	2.3081	0.9394
III	12	26	-0.4696	3.8804	0.8462
III	13	19	0.5712	2.8130	0.8421
III	14	15	0.6174	2.0571	0.8667
Level III		**273**	**0.457**	**3**	**0.908**

Table 1(a): The distribution of (y - yhat) a year ahead at all specific ages for Level I to III.

Level	Age	N	Mean(y-yhat)	SD(y-yhat)	Coverage
IV	3	7	1.0493	3.3607	0.8571
IV	4	12	0.1179	4.5186	0.8333
IV	5	23	-0.5217	1.9058	1.0000
IV	6	31	0.0808	2.8387	0.9000
IV	7	28	-0.4350	2.4152	0.9643
IV	8	20	0.7307	2.4541	0.9500
IV	9	25	2.0552	2.4368	0.8400
IV	10	36	1.1792	1.7916	1.0000
IV	11	30	-1.1096	2.9231	0.9333
IV	12	29	0.1186	3.0173	0.8621
IV	13	20	-0.2757	2.9594	0.9500
IV	14	8	-0.9527	3.9276	0.8750
Level IV		**269**	**0.195**	**2.826**	**0.925**
V	4	14	-0.6454	5.0887	0.8571
V	5	26	0.2809	4.8440	0.8846
V	6	29	0.0327	3.7600	0.8966
V	7	27	0.4738	3.5534	0.9630
V	8	25	0.8948	3.3334	0.9600
V	9	29	0.8912	2.7984	1.0000
V	10	34	1.3929	4.3637	0.8824
V	11	26	0.0733	2.3660	0.9615
V	12	22	0.8409	2.9208	0.8636
V	13	12	-0.6853	2.6660	0.9167
Level V		**244**	**0.491**	**3.654**	**0.922**

Table 1(b): The distribution of (y – yhat) a year ahead at all specific ages for Level IV and V.

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