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Gender-Specific Modeling of Growth Profiles in Pre-School-Age Children

Okul Öncesi Çocuklarda Cinsiyet-Spesifik Büyüme Profillerinin Modellemesi

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ABSTRACT Objective: In pediatric clinical trials and cohort studies, actual height, weight and head circumference of children at a specific age may be required for certain developmental assessments such as energy expenditure. This necessitates the choice of a growth model with desired characteristics to predict height and weight accurately. **Material and Methods:** To address this need, we compared Logistic and Gompertz models, which are the two most commonly used growth curve models in child development literature, using different parameterization and in a race and gender specific fashion on actual participant data from the CANDLE study, which is a prospective birth cohort of mother-child dyads in Shelby County, Tennessee, USA. We compared these competitive models and different parameterizations in terms of the size of the residuals as well as prediction standard error, for each anthropometric measurement, namely, height, weight, and head circumference. We also assessed the impact of missing data on these models. **Results:** We have shown that Gompertz model with the first or the second parameter defined with a subject-specific random effect is the best model in terms of prediction accuracy. Although the same Gompertz model fitted on each individual profile without a random effect also has similar prediction accuracy, it has inflated standard error of estimation as expected, thus, not recommended to be used. **Conclusion:** We conclude that Gompertz model with only the first or the second parameter defined with a random effect performs the best with and without missing data for height, weight, and head circumference growth in the first four years of life.

Keywords: Growth curve; growth models; early child development; first years of life; Gompertz; logistic

ÖZET Amaç: Klinik denemelerde ve kohort çalışmalarında, çocukların belli yaştaki boy, kilo ve baş çevresi, enerji harcaması gibi belli gelişim değerlendirmeleri için gerekebilir. Bu durum, boyu ve kiloyu doğru ölçmede istenilen özelliklere sahip büyüme modellerinin seçimini gerektirir. **Gereç ve Yöntemler:** Bu ihtiyaca cevap vermek için, çocuk gelişimi literatüründe en sıkça kullanılan Logistic ve Gompertz büyüme modellerini farklı parametrizasyonlarla, ırk ve cinsiyete dayalı olarak, ABD Tennessee Eyaleti, Shelby ilçesinden 'the CANDLE' çalışması adındaki, anne-çocuk doğum kohortunun verilerini kullanarak karşılaştırdık. Bu birbirine rakip modelleri, farklı parametrizasyonlar altında, her bir antropometrik ölçüm icin (boy, kilo ve baş çevresi), artıkların büyüklüğü ve tahmin standart hatası açısından karşılaştırdık. Ayrıca kayıp gözlemlerin bu modeller üzerindeki etkisini değerlendirdik. **Bulgular:** Birinci veya ikinci parametresi denek-spesifik rastgele-etki olarak tanımlanan Gompertz modelinin, tahmin doğruluğu açısından en iyi model olduğunu gösterdik. Her bir denek için, rastgele-etki parametresi olmadan kurulan aynı Gompertz modeli de, benzer bir tahmin doğruluğuna sahip olmakla birlikte, beklendiği gibi şişirilmiş standart hata verdiği için, kullanılması tavsiye edilmedi. **Sonuç:** Sadece birinci veya ikinci parametresi denek-spesifik rastgele-etki olarak tanımlanan Gompertz modelinin, yaşamın ilk dört yılında, boy, kilo ve baş çevresi büyümesi modellemesinde, kayıp gözlem altında bile, en iyi performansı gösterdiği sonucuna vardık.

Anahtar kelimeler: Büyüme eğrisi; büyüme modelleri; erken çocuk gelişimi; yaşamın ilk yılları; Gompertz; lojistik

In pediatric clinical trials and cohort studies, actual anthropometric measures such as height and weight, may be needed for specific developmental evaluations. For example, we may need the height and weight of an infant at age 9-month or at 30-month for energy expenditure calculations. Although such studies pre-specify visit times like 1-year, 2-year, etc., such visits may not take place at the time they are scheduled (for example, a 24-month visit may be performed on 27-month) or may be totally missed by the study participants, while we

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may still need the anthropometric measures exactly at 24-months, or 30 months, etc, for developmental assessments. This necessitates that a growth curve model (GCM) that has acceptable prediction accuracy for the existing measures and can provide anthropometrics predictions for specific times with as less prediction as possible.

To address this modelling issue, growth standard profiles were developed for specific populations such as by Center for Disease Control (CDC) for the US population in 1970s, Ozturk et al. in 2011 for Turkish pediatric population, and for global population as well.[1-13] Now, with the guidance of these standard curves, the remaining issue is how to choose a statistical modelling framework that would predict the needed anthropometrics at a given time with the least prediction error possible.

In this study, we will compare two GCMs in terms of prediction accuracy, prediction error, and performance under missingness. We will first present these two models, namely, Gompertz GCM and Logistic GCM in a random-effect modelling parametrization. We will then apply these methods to a real-life pediatric cohort study and measure the prediction accuracy and error under various parametrization. We will then compare the models in terms of their performance under missingness.

MATERIAL AND METHODS

Kocak (2017) provides the details and different parametrizations of the Gompertz GCM and Logistic GCM functions and here we shortly introduce them again. In this study, we again used only Logistic and Gompertz growth functions as these two are the ones most commonly used to describe child growth and the other growth curves such as the Brody growth curve, the von Bertalanffy growth curve, or (negative) exponential growth curve are mainly used for animal growth and not necessarily suitable for child development especially in early years of life as indicated by Karkach (2006) with mathematical justifications and historical development of how different versions of Logistic and Gompertz models evolved over time to describe human growth, specifically child growth.[14-17]

GOMPERTZ MODEL

Winsor (1932) proposed the following function to model growth profiles:

$$y_{ij} = \beta_1 exp\left\{exp(\beta_2)\frac{exp(\beta_3 t_{ij})-1}{\beta_3}\right\} + \varepsilon_{ij}, (1)$$

where y_{ij} is the anthropometric measure for subject-i at time t_{ij}. t_{ij} denotes the measurement times, which may change subject to subject.[18] In this parameterization, β_1 represents the asymptote of the growth curve at maturity (i.e., when age goes to infinity), β_2 is a type of a shape parameter that affects the initial growth rate, upper asymptote and infection time, and β_3 is another shape parameter that also affects the initial growth rate and upper asymptote.

By adding specific random deviation (i.e., random effects) to each model parameter in (1), we can turn this non-linear model to non-linear random effect model as follows:

$$y_{ij} = (\beta_1 + \beta_{1i}) exp\left\{exp(\beta_2 + \beta_{2i})\frac{exp\left((\beta_3+\beta_{3i})t_{ij}\right)-1}{\beta_3+\beta_{3i}}\right\} + \varepsilon_{ij}\ . (2)$$

LOGISTIC GCM

Lindstrom and Bates (1990) and Pinheiro and Bates (1995) proposed the following logistic nonlinear model:

$$y_{ij} = \frac{\beta_1}{1+exp\left\{\frac{-(t_{ij}-\beta_2)}{\beta_3}\right\}} + \varepsilon_{ij},\ (3)$$

where y_{ij} is the anthropometric measure in subject-i at time t_{ij}.[19] The parameter interpretation is similar to those for the parameters of Gompertz model.

As earlier in Gompertz GCM, by adding specific random deviation (i.e., random effects) to each model parameter in (3), we can turn this non-linear model to non-linear random effect model as follows:

$$y_{ij} = \frac{\beta_1+\beta_{1i}}{1+exp\left\{\frac{-\left(t_{ij}-(\beta_2+\beta_{2i})\right)}{(\beta_3+\beta_{3i})}\right\}} + \varepsilon_{ij}, (4)$$

The models both in (2) and (4) have three fixed parameters and three random parameters.

Kocak used the following parametrizations to compare and contrast these two GCMs, using the US and Turkish growth charts, specifically, the 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 97th percentiles:[20]

- Individual profile modelling: None of β_1, β_2 and β_3 had random effects; (M0);
- β_1 is defined with random effect $(\beta_1 + \beta_{1i})$ (M1);
- β_2 is defined as a random effect $(\beta_2 + \beta_{2i})$ (M2);
- β_3 is defined as a random effect $(\beta_3 + \beta_{3i})$ (M3) ;
- β_1 and β_2 are defined as random effects (M4);
- β_1 and β_2 are defined as random effects (M5);
- β_2 and β_3 are defined as random effects (M6);
- All β_1, β_2 and β_3 are defined as random effects (M7);

The NLIN procedure of SAS ® Version 9.4 was used to model the individual profiles with no random effect (M-0). The NLMIXED procedure in SAS® version 9.4 were used to fit the other non-linear random-effects models (M1 through M7)

In this study, we followed a similar approach to compare the performance of these two approaches under different parameter combinations such as Model-0 through Model-7 above. Specifically, from each model, we recorded the model convergence status under each model run, captured the predicted values for each anthropometric measurement of interest, namely, height, weight, and head circumference, at all time points contributing to the model, and the standard errors of predictions.

We first summarized the model convergence status of the competing models. We then summarized these summary prediction measures as 'absolute residuals' representing the absolute departure of the predicted values from the correct measures; while we recognize that this is not a mainstream approach for model comparison, we chose it as the prediction accuracy is of the primary importance due to the fact that other computations such as energy expenditure depends on accurate estimation of unknown growth measure and comparing the models in terms of absolute residuals makes more sense. Along the same line, we also summarized the prediction standard errors and compare across models. In our summaries, we used median as a more robust summary measure for absolute residuals and prediction standard errors.

To compare the prediction characteristics of the above models further under missingness, we induced missingness at birth (Year-0), at Year-2, and at Year-4.

This research has been conducted in line with the Helsinki Declaration principles.

CANDLE DATA

The Conditions Affecting Neurocognitive Development in Early Childhood (CANDLE) study, based at the University of Tennessee Health Sciences Center (UTHSC), is a prospective prenatal cohort study that recruited model-child dyads in Memphis (Shelby County), Tennessee. A detailed description of the cohort design, inclusion criteria, participant recruitment and cohort follow-up has been published previously.[21-23] The study enrolled 1503 healthy pregnant mothers who are 16-40 years of age during their 2nd trimester (16-28 weeks of gestation) between 2006 and 2011. Of these, 1462 participated in a study visit at delivery of which 1455 had a live-births. The CANDLE study originally scheduled clinic visits at the time of delivery, and when the CANDLE child was 1, 2, 3, and 4-years old. The study is still continuing with much later scheduled visits. The CANDLE study received its first institutional review board (IRB) approval on 4/28/2006 and has kept its IRB approvals current throughout the study. At each visit, the anthropometric measures, namely, height (length for the infant), weight, and head circumference, were obtained. For the first two years of life, the clinic measurement for height is actually captured as 'length' and in this particular study, we combined the length measurements from the first two years of life and the height measurements from year-3 and year-4 to represent the height profile of a given participant. We presented the anthropometric measures summaries by gender and race in Table 1.

TABLE 1: Anthropometric measures summaries overall and by gender and race.

		Weight (kg)			Height (cm)			Head circumference (cm)		
		N	Mean	StdDev	N	Mean	StdDev	N	Mean	StdDev
Overall	**Birth**	1454	3.2	0.6	1409	50.1	3.1	1399	33.8	2.0
	Year-1	1127	10.3	1.3	1123	76.3	3.5	1109	46.8	1.6
	Year-2	1089	13.0	1.7	1076	87.8	3.7	1066	48.9	1.6
	Year-3	1032	15.3	2.2	1020	96.2	4.1	1022	49.6	3.7
	Year-4	1073	18.7	3.9	1067	106.2	6.0	1075	50.9	2.5
Male	**Birth**	734	3.3	0.6	711	50.3	3.2	700	33.9	2.1
	Year-1	566	10.6	1.3	566	76.8	3.4	556	47.3	1.5
	Year-2	549	13.3	1.7	544	88.0	3.6	539	49.4	1.6
	Year-3	508	15.6	2.2	504	96.6	4.0	507	50.0	3.7
	Year-4	533	18.8	3.6	531	106.4	5.9	535	51.2	2.6
Female	**Birth**	720	3.2	0.5	698	49.9	2.8	699	33.6	1.9
	Year-1	561	9.9	1.2	557	75.7	3.4	553	46.2	1.5
	Year-2	540	12.7	1.7	532	87.5	3.9	527	48.4	1.5
	Year-3	524	15.0	2.3	516	95.9	4.1	515	49.2	3.6
	Year-4	540	18.6	4.1	536	106.1	6.0	540	50.6	2.3
Black/African American	**Birth**	953	3.1	0.6	922	49.6	3.2	913	33.4	2.0
	Year-1	707	10.3	1.3	703	76.4	3.4	697	46.7	1.6
	Year-2	694	12.9	1.7	687	87.7	3.7	678	48.9	1.6
	Year-3	676	15.3	2.4	668	96.3	4.0	667	49.6	3.3
	Year-4	726	19.0	4.2	725	106.8	6.2	730	50.9	2.8
White	**Birth**	472	3.4	0.5	460	51.0	2.6	460	34.4	1.7
	Year-1	399	10.2	1.2	399	76.0	3.4	392	46.8	1.6
	Year-2	375	13.1	1.6	369	88.0	3.8	368	49.1	1.6
	Year-3	339	15.3	1.9	336	96.0	4.1	338	49.7	4.1
	Year-4	330	18.1	2.9	325	105.1	5.2	328	51.1	1.6

kg: Kilogram, cm: Centimeter, StdDev: Standard deviation.

RESULTS

In the mixed-effects non-linear models, one of the challenges that we face is the issue of convergence. Therefore, we first assess whether or not the convergence is an issue for a given model especially when we increase the number of random parameters in the model (Table 2). We observe that the convergence issue is much bigger for the Logistic GCM with two or three parameters defined with random effects ($\boldsymbol{\beta_1}$ and $\boldsymbol{\beta_3}$ as random factors, $\boldsymbol{\beta_2}$ and $\boldsymbol{\beta_3}$ as random factors) while Gompertz GCM had convergence issue only when all parameters were defined with their random effects. Based on these observations, we reduce our comparison to individual-fit model (M0) and one-random effect models (M1-M3).

Individual-profile model (M0) resulted in smaller prediction residual compared Gompertz and Logistic GCMs with only one-random effect (M1-M3), where Gompertz Models provided much more favorable model fit both in terms of the size of residuals as well as prediction standard error (Table 3, Table 4, Figure 1, Figure 2, Figure 3, Figure 4). Model-1 and Model-2 were the best competitors to the individual fit model, and Model-2 had better fit properties in terms of standard error of estimation (Table 3, Figure 2, Figure 4). For head circumference, we observed similar findings as well (Table 2, Table 3, Table 4 and Figure 5, Figure 6). Individual-fit models had much higher standard error of estimation as expected due to the fact that it

TABLE 2: Model Convergence Summaries (X Represents Models That Had No Convergence Issues).

			Individual fit		β_1 as a random factor		β_2 as a random factor		β_3 as a random factor		β_1 and β_2 as random factors		β_1 and β_3 as random factors		β_2 and β_3 as random factors		β_1 and β_2 and β_3 as random factors	
			Logistic	Gompertz	Logistic	Gompertz	Logistic	Gompertz	Logistic	Gompertz	Logistic	Gompertz	Logistic	Gompertz	Logistic	Gompertz	Logistic	Gompertz
Height	5 Time-points	M	X	X	X	X	X	X	X	X	X	X		X		X		X
		F	X	X	X	X	X	X	X	X	X	X		X		X		X
	4 Time-points	M	X	X	X	X	X	X	X	X	X	X		X		X		X
		F	X	X	X	X	X	X	X	X	X	X		X		X		X
Weight	5 Time-points	M	X	X	X	X	X	X	X	X	X	X		X		X		
		F	X	X	X	X	X	X	X	X	X	X		X		X		
	4 Time-points	M	X	X	X	X	X	X	X	X	X	X		X				
		F	X	X	X	X	X	X	X	X	X	X		X		X		
Head Circ.	5 Time-points	M	X	X	X	X	X	X	X	X	X	X		X		X		X
		F	X	X	X	X	X	X	X	X		X		X		X		
	4 Time-points	M	X	X	X	X	X	X	X	X	X	X		X		X		X
		F	X	X	X	X	X	X	X	X	X	X		X		X		

M: Male, F: Female, Head Circ.: Head Circumference.

TABLE 3: Comparisons of model performance for modeling height, weight, and head circumference (median absolute residual).

Median |Residual|			All		M		F		AA		CA	
			L	G	L	G	L	G	L	G	L	G
Height	Complete data (5-Time points)	Individual fit	1.76	1.46	1.73	1.44	1.79	1.48	1.90	1.59	1.47	1.18
		B1 as random	2.10	1.87	2.05	1.83	2.17	1.91	2.23	1.98	1.85	1.68
		B2 as random	2.63	1.89	2.58	1.86	2.71	1.90	2.71	2.00	2.37	1.64
		B3 as random	2.25	1.96	2.20	1.94	2.26	1.97	2.41	2.09	1.92	1.76
	Complete data (4-Time points)	Individual fit	1.55	1.31	1.55	1.28	1.57	1.33	1.72	1.43	1.29	1.10
		B1 as random	2.10	1.89	2.12	1.90	2.09	1.92	2.20	1.99	1.85	1.71
		B2 as random	2.61	1.91	2.60	1.88	2.65	1.91	2.72	1.99	2.30	1.71
		B3 as random	2.23	1.96	2.22	1.95	2.21	1.97	2.36	2.03	1.94	1.82
Weight	Complete data (5-Time points)	Individual fit	0.79	0.62	0.80	0.63	0.78	0.61	0.84	0.66	0.69	0.54
		B1 as random	0.83	0.67	0.85	0.67	0.82	0.68	0.89	0.72	0.76	0.61
		B2 as random	1.20	0.70	1.17	0.70	1.20	0.70	1.23	0.76	1.11	0.64
		B3 as random	8.24	0.73	8.45	0.71	7.96	0.73	8.19	0.79	0.96	0.67
	Complete data (4-Time points)	Individual fit	0.67	0.52	0.70	0.52	0.66	0.51	0.73	0.56	0.60	0.44
		B1 as random	0.82	0.66	0.82	0.66	0.80	0.66	0.86	0.69	0.74	0.59
		B2 as random	1.17	0.68	1.18	0.67	1.16	0.67	1.22	0.73	1.05	0.60
		B3 as random	1.05	0.70	1.07	0.68	7.51	0.67	1.09	0.73	0.97	0.63
Head circumference	Complete data (5-Time points)	Individual fit	0.24	0.23	0.23	0.21	0.26	0.24	0.24	0.22	0.24	0.23
		B1 as random	0.79	0.79	0.77	0.77	0.80	0.78	0.75	0.74	0.74	0.73
		B2 as random	1.39	0.81	1.14	0.78	1.43	0.79	1.22	0.81	1.64	0.72
		B3 as random	1.31	0.80	1.13	0.78	1.39	0.76	1.13	0.81	1.56	0.71
	Complete data (4-Time points)	Individual fit	0.24	0.23	0.23	0.21	0.26	0.24	0.24	0.22	0.24	0.23
		B1 as random	0.79	0.79	0.77	0.77	0.80	0.78	0.75	0.74	0.74	0.73
		B2 as random	1.39	0.81	1.14	0.78	1.43	0.79	1.22	0.81	1.64	0.72
		B3 as random	1.31	0.80	1.13	0.78	1.39	0.76	1.13	0.81	1.56	0.71

M: Male, F: Female, AA: African American, CA; Caucasian American, L: Logistic Growth Curve, G: Gompertz Growth Curve.

TABLE 4: Comparisons of model performance for modeling height, weight, and head circumference (median standard error of estimation).

Median standard error of estimation			All		M		F		AA		CA	
			L	G	L	G	L	G	L	G	L	G
Height	Complete data (5-Time points)	Individual fit	3.83	3.28	3.77	3.18	3.97	3.37	4.13	3.53	3.22	2.77
		B1 as random	1.14	1.07	1.10	1.03	1.18	1.12	1.16	1.10	1.08	1.01
		B2 as random	0.83	0.96	0.82	0.94	0.86	1.01	0.85	1.00	0.87	0.91
		B3 as random	1.08	0.92	1.05	0.89	1.13	0.97	1.10	0.94	1.04	0.90
	Complete data (4-Time points)	Individual fit	3.61	3.06	3.60	3.04	3.62	3.08	3.95	3.36	3.04	2.61
		B1 as random	1.16	1.09	1.15	1.08	1.17	1.10	1.18	1.11	1.10	1.04
		B2 as random	0.87	1.00	0.85	0.99	0.90	1.01	0.87	1.02	0.90	0.95
		B3 as random	1.10	0.94	1.08	0.95	1.13	0.96	1.12	0.96	1.07	0.93
Weight	Complete data (5-Time points)	Individual fit	1.69	1.31	1.72	1.32	1.66	1.28	1.79	1.41	1.48	1.14
		B1 as random	0.48	0.42	0.46	0.40	0.48	0.43	0.51	0.45	0.42	0.36
		B2 as random	0.44	0.37	0.37	0.36	0.47	0.37	0.51	0.40	0.38	0.33
		B3 as random	0.26	0.36	0.30	0.36	0.30	0.36	0.27	0.39	0.54	0.33
	Complete data (4-Time points)	Individual fit	1.56	1.20	1.62	1.22	1.51	1.18	1.67	1.29	1.40	1.08
		B1 as random	0.47	0.41	0.46	0.39	0.48	0.43	0.50	0.44	0.42	0.36
		B2 as random	0.41	0.37	0.28	0.36	0.50	0.37	0.46	0.39	0.37	0.33
		B3 as random	0.61	0.36	0.54	0.35	0.21	0.36	0.67	0.38	0.51	0.33
Head circumference	Complete data (5-Time points)	Individual fit	0.80	0.73	0.76	0.69	0.83	0.76	0.78	0.71	0.81	0.75
		B1 as random	0.78	0.78	0.71	0.71	0.79	0.79	0.70	0.70	0.84	0.84
		B2 as random	0.09	0.70	0.11	0.65	0.15	0.73	0.10	0.63	0.20	0.77
		B3 as random	0.09	0.69	0.11	0.64	0.14	0.71	0.26	0.62	0.18	0.74
	Complete data (4-Time points)	Individual fit	0.80	0.73	0.76	0.69	0.83	0.76	0.78	0.71	0.81	0.75
		B1 as random	0.78	0.78	0.71	0.71	0.79	0.79	0.70	0.70	0.84	0.84
		B2 as random	0.09	0.70	0.11	0.65	0.15	0.73	0.10	0.63	0.20	0.77
		B3 as random	0.09	0.69	0.11	0.64	0.14	0.71	0.26	0.62	0.18	0.74

M: Male, F: Female, AA: African American, CA; Caucasian American, L: Logistic Growth Curve, G: Gompertz Growth Curve.

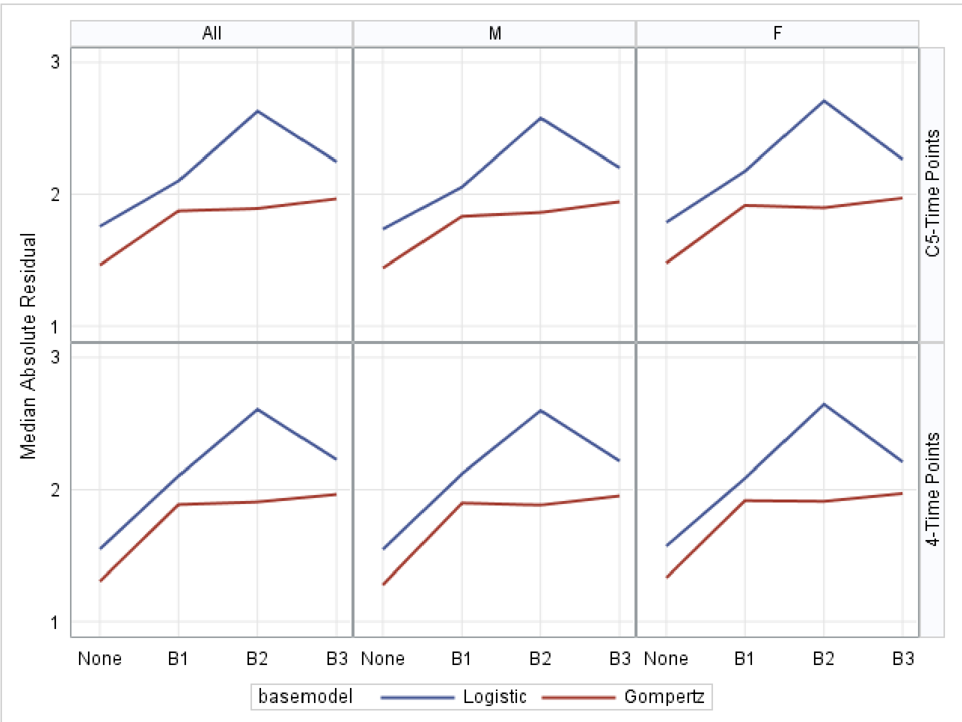

FIGURE 1: Median absolute residuals for height (M: Male, F: Female).

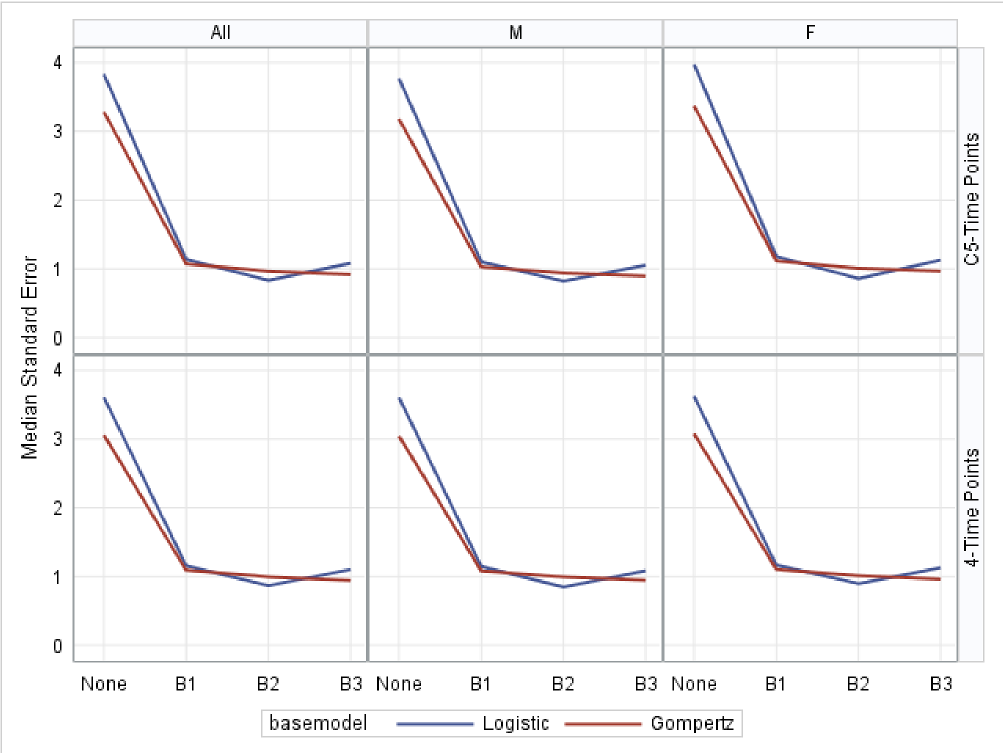

FIGURE 2: Median estimation standard error for height (M: Male, F: Female).

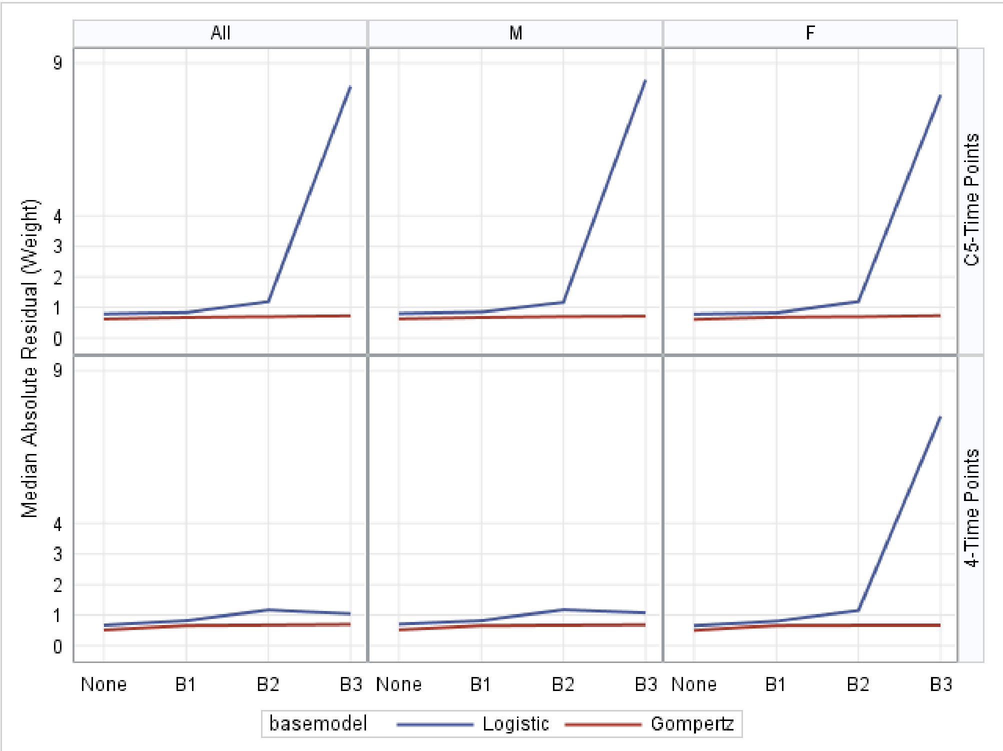

FIGURE 3: Median absolute residual for weight (M: Male, F: Female).

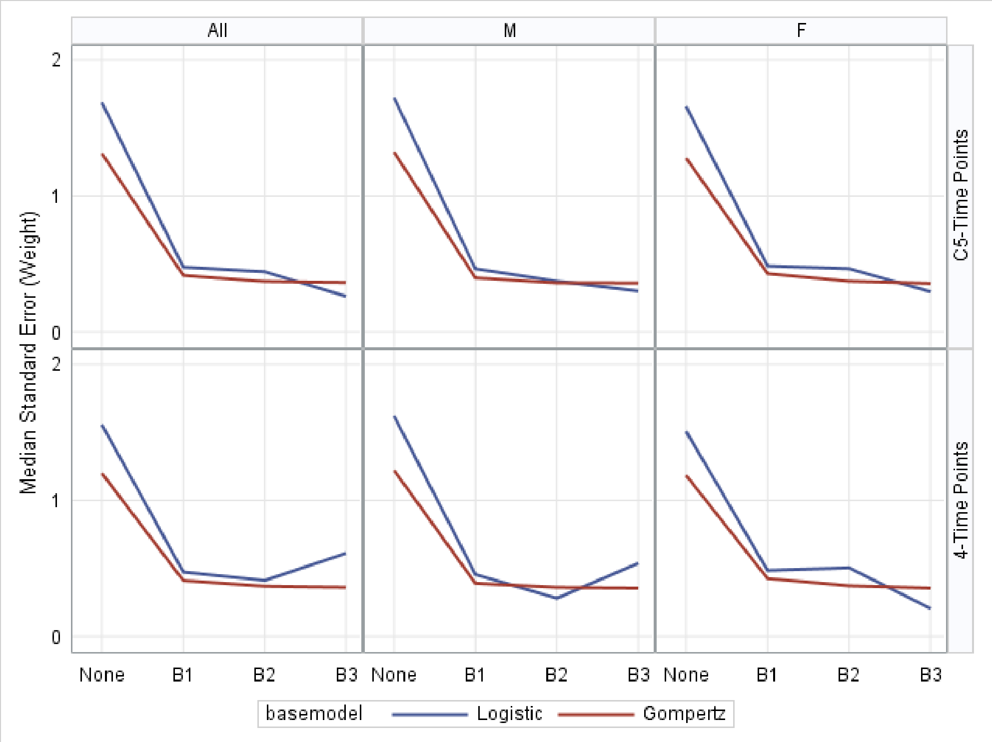

FIGURE 4: Median estimation standard error for weight (M: Male, F: Female).

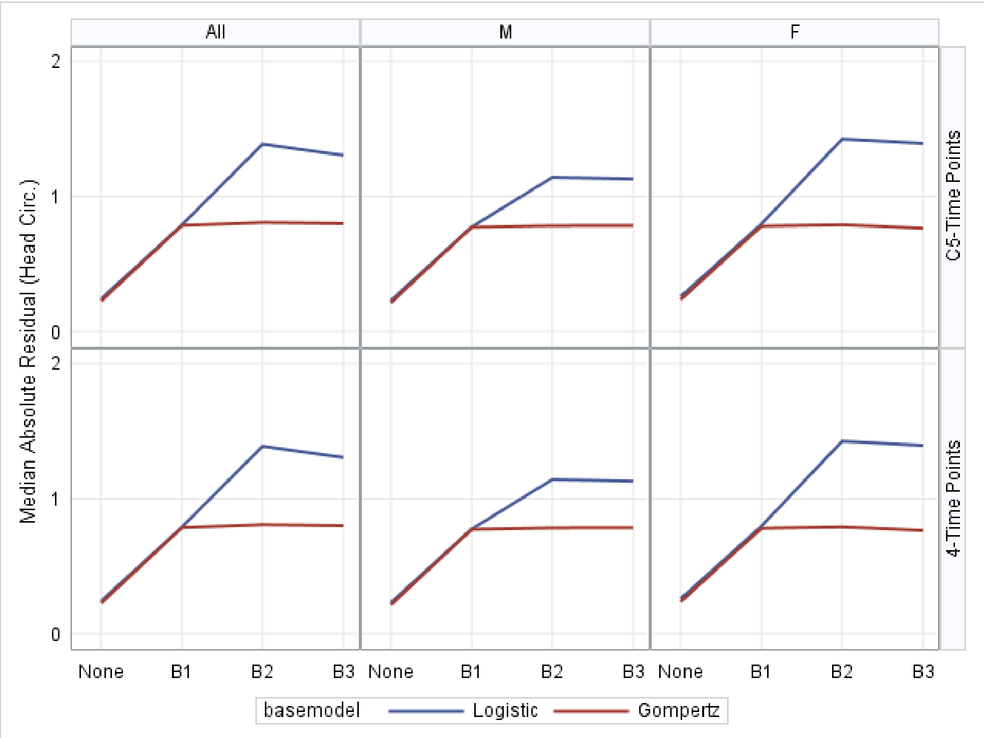

FIGURE 5: Median absolute residual for head circumference (M: Male, F: Female).

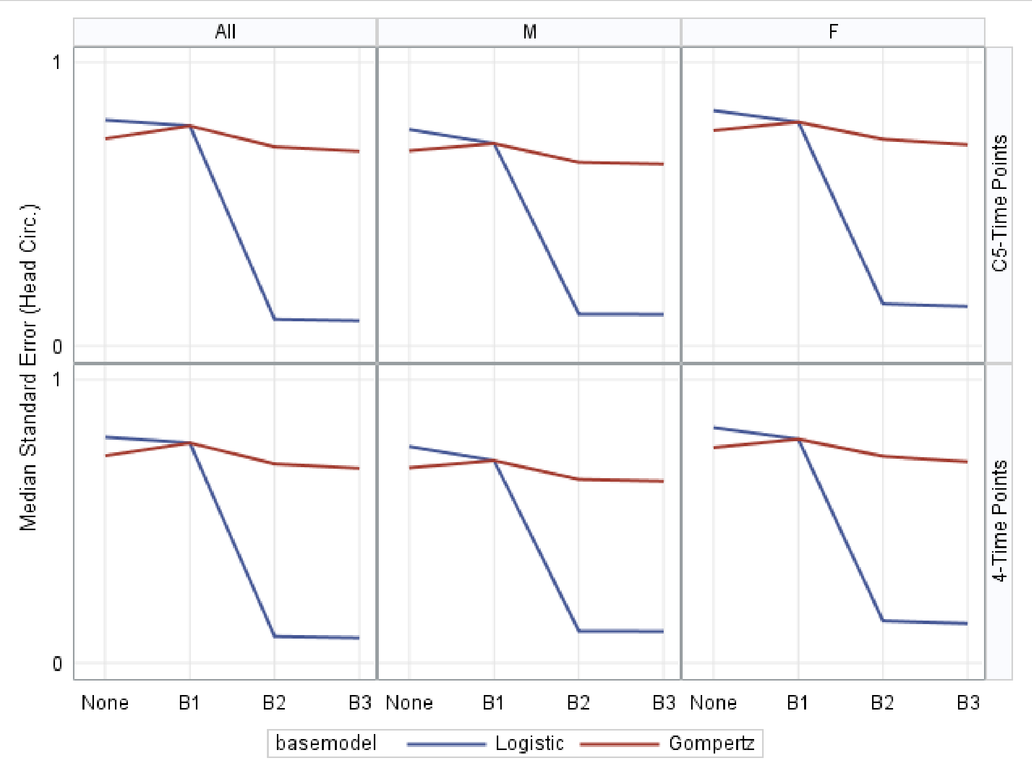

FIGURE 6: Median estimation standard error for head circumference (M: Male, F: Female).

utilized the growth data of a single individual alone, while other models utilized the entire growth data, where individuals were treated as independent clusters, and in the prediction of a growth profile of an individual, data was borrowed from all his or her peers. This same conclusion is valid for gender specific, race specific (not shown), and gender-race specific models (not shown), and under both Logistic and Gompertz-based models.

We also aimed to compare these GCMs in model performance under missingness. More specifically, we planned to assess the impact of missingness at birth (year-0), at year-2, and at year-4. Due to the obvious reason of model fitting needs, we have done this only with children having growth data from all five points under investigation, namely, from year-0 to year-4, as when one data point was forced to be missing, we are left with only 4 measurements, and anything less than this causes expected convergence issues with these models, especially with the individual fit model.

The results of these model comparisons under missingness are provided in Table 5 and Table 6 both for height and weight predictions, and they confirm our conclusions with the complete data. Not surprisingly, individual fit models now lose its advantage of having the more favorable absolute residuals as Model-1 and Model-2 have smaller departure from the 'missing' growth measurement under missingness.

Based on these observations we propose Model-1 (i.e., the model with only β_1 having a random effect $(i.e., \beta_1 + \beta_{1i})$) and Gompertz Model-2 (i.e., the model with only β_2 having a random effect $(i.e., \beta_2 + \beta_{2i})$) as best models when modeling growth data for the early years of life (up to year 4 in our sample in this work).

TABLE 5: Results with missingness at selected time points for height and weight.

Median |Residual| (Cells with no estimate indicate convergence issues)			Logistic				Gompertz			
			Individual fit	B1 as random	B2 as random	B3 as random	Individual fit	B1 as random	B2 as random	B3 as random
Year-0 missing	Height	All	12.94	.	.	.	12.37	11.89	11.53	10.92
		M	13.10	12.87	12.80	12.66	12.48	12.41	11.46	10.86
		F	12.66	12.57	12.52	12.38	12.17	11.35	11.24	10.63
	Weight	All	4.36	4.23	4.37	.	4.10	4.03	.	.
		M	4.58	4.46	4.63	4.62	4.32	4.24	3.95	3.14
		F	4.14	4.12	4.14	.	3.88	3.81	3.82	.
Year-2 missing	Height	All	3.05	3.14	3.18	3.17	2.53	2.56	2.64	2.86
		M	3.31	3.99	3.39	3.38	2.67	2.63	2.72	2.97
		F	2.66	3.28	2.94	2.93	2.30	2.39	2.55	2.63
	Weight	All	1.57	1.89	1.80	1.76	1.04	1.05	1.09	1.17
		M	1.69	2.02	1.93	1.78	1.13	1.18	.	1.32
		F	1.37	1.72	1.64	1.67	0.98	0.92	0.98	1.06
Year-4 missing	Height	All	6.38	6.57	6.58	6.57	5.51	5.20	5.44	5.47
		M	6.17	6.25	6.32	6.30	5.29	5.32	5.42	5.32
		F	6.52	6.90	6.95	6.94	5.66	5.13	5.45	5.61
	Weight	All	2.64	2.57	2.57	2.59	2.21	2.06	2.10	2.25
		M	2.56	2.43	2.43	2.45	2.13	2.03	2.08	2.23
		F	2.68	.	2.69	.	2.29	2.08	2.16	2.33

M: Male, F: Female.

TABLE 6: Median standard error (SE) of predictions under missingness for height and weight.

Median SE (Cells with no estimate indicate convergence issue			Logistic				Gompertz			
			Individual fit	B1 as random	B2 as random	B3 as random	Individual fit	B1 as random	B2 as random	B3 as random
Year-0 missing	Height	All	3.14	.	.	.	3.62	0.72	0.33	0.39
		M	2.88	1.30	1.41	0.98	3.45	0.72	0.42	0.51
		F	3.41	1.21	1.43	0.95	4.02	0.83	0.49	0.57
	Weight	All	0.58	0.22	0.76	.	0.75	0.22	.	.
		M	0.59	0.21	1.05	0.59	0.76	0.21	0.12	0.17
		F	0.56	0.74	1.08	.	0.75	0.25	0.12	.
Year-2 missing	Height	All	4.51	0.45	0.41	0.45	3.66	1.28	1.21	0.90
		M	4.40	0.61	0.57	0.60	3.48	1.21	1.17	0.88
		F	4.66	0.63	0.59	0.63	3.89	1.34	1.25	0.92
	Weight	All	1.97	0.50	0.25	0.35	1.58	0.54	0.48	0.40
		M	1.89	0.65	0.36	0.45	1.51	0.51	.	0.40
		F	2.11	0.75	0.34	0.64	1.64	0.56	0.48	0.38
Year-4 missing	Height	All	3.49	0.67	0.67	0.62	3.14	1.33	1.69	2.23
		M	3.62	0.93	0.93	0.87	3.39	1.27	1.61	2.11
		F	3.30	0.94	0.96	0.88	3.01	1.41	1.76	2.33
	Weight	All	1.35	0.44	0.53	0.50	1.12	0.50	0.53	0.65
		M	1.37	0.62	0.73	0.69	1.12	0.48	0.51	0.62
		F	1.32	.	0.77	.	1.11	0.50	0.54	0.66

M: Male, F: Female.

DISCUSSION

In birth cohort studies, one of the key components is the anthropometric measurements obtained starting from birth (potentially even pre-birth in the womb). Naturally, growth profiles differ by various factors including gender, race, etc. This requires that growth profiles be described through functions flexible enough to capture such variations with subgroups of pediatric populations as well as within each individual. In this study, we compared two such growth functions, namely, Logistic and Gompertz functions, and we increased the flexibility of these functions by adding random effects that will capture the individual growth characteristics. As always, with the added additional parameters comes the cost, the potential model convergence issues. Such concerns become negligible with the fact that the addition of these random effects to the model now opens up the opportunity to use a mixed-effect modeling framework, which is very powerful as it utilizes the entire data (i.e., data from all individuals) even when we intend to make predictions on one individual, in a way borrowing data from the peers of the targeted individual. In this work, we designed our analysis approach to compare all such competing models under Logistic and Gompertz growth functions.

We have shown that overall Gompertz models displayed much better model fitting characteristics compared to Logistic models both in terms of prediction accuracy and standard error. For both modeling framework, adding more than one random effect to the underlying models did not improve the model fit and moreover caused serious converge issue. Therefore, after the initial evaluation, we turned our attention to individual fit, and one-random effect models. Although individual fit models performed best under the complete data setting (i.e., having complete data for all give time points), it came with a price of increased standard error of estimation. This is an expected phenomenon in model fitting as the individual fit models utilize data from a single individual alone, and performs the model fitting each and every individual independently of his her peers in the same cohort. On the other hand, one-random effect models we used (namely, Model-1 to Model-3) are part of mixed-effects models where fixed parameters describe the behavior of the underlying population and random effect provide the needed individual specific variations, and such models utilize the entire data from the cohort at hand.

All these models pose a general issue of model convergence especially under scarce data. As stated above, this is more of the case with more specific models, that is, models having more fixed and random effects. To tackle this issue, we suggest that the model parameter estimates from the simpler models be added to the search grid of the more complicated models so that the initial values provided to the non-linear modeling are closer to where the true parameters are. Otherwise, the practitioner has to define a very wide and fine search grids to achieve model convergence and this can be costly. This becomes more of the case under missingness.

We also compared the convergence and model fitting characteristics of our competing models under missingness. To make it more practical, we deleted the growth measure at birth, which represents a severe scenario that no birth data exists, we deleted the year-2 growth measure, which represents a mild scenario that some data missing between available growth measures, and we deleted the year-4 growth measure, which represents the ending value of the growth profile when the first four hears of life considered. Not surprisingly, the highest departure of the prediction from the true growth measure was observed under the missingness at year-0, followed by year-4, and not surprisingly, the smallest departure was observed for year-2, as the growth profile was able to be estimated with the available growth measures from earlier and later time points. Under missingness as well, Gompertz approach was superior to Logistic approach.

All these led us to conclude that Gompertz Model with random effects related to first or second parameter (i.e., Model-1 and Model-2) are much better alternatives to individual fit models. Practitioners may choose to start with Model-1 as Model-2 seems to be more prone to convergence issues, although it was negligible in this application.

We plan to expand this research to run simulation studies exploring through with model parameters we can introduce factors that may influence the growth profiles, thus generating a statistical testing framework to test the significance of such factors. When the growth time window is a short one, such as first 3-years of life, first 5-years of life, etc., and when the prediction need is of interpolation rather than extrapolation, we plan to investigate linear-modeling approach with a cubic or higher order fit as well. We then plan to implement such results on the CANDLE growth data again.

CONCLUSION

We conclude that in predicting early childhood anthropometric measures, Gompertz GCM with only the first or the second parameter defined with a random effect performs the best with and without missing data. Although individual Gompertz GCM has better average predictions, it suffers from inflated prediction errors.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

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