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Mebrahtu, TF, Feltbower, RG, Petherick, ES et al. (1 more author) (2015) Growth patterns of white British and Pakistani children in the Born in Bradford cohort: a latent growth modelling approach. Journal of Epidemiology and Community Health, 69 (4). pp. 368-373. ISSN 0143-005X

https://doi.org/10.1136/jech-2014-204571

Growth patterns of White British and Pakistani children in the Born in Bradford cohort: a latent growth modelling approach.

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Abstract:

BACKGROUND: Childhood growth patterns have been proposed as a key predictor of health during childhood and adult life. In earlier studies however, the statistical methodologies employed failed to uncover the more subtle patterns in growth trajectories.

METHODS: Study participants were 1364 singleton term children (602 White British and 762 Pakistani origin) drawn from the Born in Bradford (BiB) prospective cohort. Weights were measured at 0, 1, 3, 6, 12, 18, 24, and 36 months. Age- and Sex-specific standardised weight scores were derived based on the World Health Organisation growth standards. Missing growth data were estimated using Full Information Maximum Likelihood (FIML). Growth Mixture Modelling was used to analyse growth patterns of children from birth until 36 months.

RESULTS: On average, Pakistani children were 190 grams lighter than White British children at birth. Based on our growth mixture model results, the study children had three distinct growth patterns: ‘normal growers’ (95.9%), ‘fast growers’ (2.5%) and ‘slow growers’ (1.6%). The Pakistani children were more likely to be in either the ‘fast’ (OR=2.90; 95% CI: 0.91, 9.25) or ‘slow’ (OR=15.63; 95% CI: 1.06, 230) growers class than the White British. Pakistani children showed faster growth than White British children between 3 and 36 months of age.

CONCLUSION: In this growth study we have identified that the study children have three distinct growth patterns. These growth patterns may provide greater insight in predicting the risk of childhood or early adulthood diseases in life-course studies.

What is known on this topic:
➢ Birth weight and early childhood growth are predictors of childhood and adulthood health. ➢ Pakistani children are lighter at birth than white British infants. ➢ The growth patterns of Pakistani and white British children are unknown.
What this study adds:
➢ Pakistani and white British children have three distinct growth patterns—'Normal', 'fast' and 'slow' growers. ➢ Pakistani children are more likely to be in either the 'fast' or 'slow' growers group than white British children. ➢ Identification of the distinct growth patterns of Pakistani and white British children may provide greater insight in predicting the risk of childhood or early adulthood diseases.

Word count: 2810.

Key words: Growth patterns, childhood growth, latent growth modelling, growth trajectories.

INTRODUCTION

Childhood growth patterns have been reported as predictors of health during early childhood and adult life. For example, lower birth weight associated with higher growth rates during early childhood and adulthood has been related to hypertension,[1-3] chronic heart disease [4 5] diabetes,[6] and asthma.[7] However, except for Rzehak et al,[7] multiple regression approaches were used which are prone to collinearity problems caused by the repeated weight measurements.[8 9] Also multiple regression only provides an estimate of the overall growth change over time which does not take into account individual subject variability.[9]

Recently, multilevel spline modelling has been used to estimate growth trajectories.[10 11] Multilevel splines, which are equivalent to multi-group Latent Growth Curve modelling, do account for the individual variation in growth by including random coefficients (i.e. slope and intercept) in the models. However, these modeling techniques assume homogeneity of growth patterns in a population which may not be realistic in practice.[12] For example, suppose that we want to know the growth trajectories of children from two different schools. In both multilevel spline and latent growth curve modeling, measurement occasions are nested within individuals, who are nested within schools. The two models will test if there is a difference in growth trajectories of the two schools' children. We will thus only have two mean growth trajectories to compare. In other words, these models cannot differentiate between more than one distinct growth trajectories within each school. In order to test whether the homogeneity assumption holds, one has to implement growth mixture modeling.[12 13]

To test whether there is heterogeneity of growth patterns in the BiB1000 population, we have firstly implemented Latent Growth Curve modelling and then fitted a Growth Mixture Model to the dataset to account for the between and within group growth pattern variability.[12 13]

METHODOLOGY

STUDY DESIGN AND PARTICIPANTS

The Born in Bradford study is a prospective cohort, mainly bi-ethnic, that examines the impact of environmental, genetic and social factors on health of the population of Bradford.[14] The methods of recruitment are explained in detail elsewhere.[10 15] Recruitment of participants started in March 2007 and ended in December 2010; a total of 13,776 pregnant mothers were recruited. At the same time, a sub cohort (BiB1000) of 1,735 mothers and 1763 babies were also recruited for follow-up examinations, i.e., 1707 singletons and 28 twins. Ethical approval for the Born in Bradford project has been granted by Bradford Research Ethics Committee (Ref 07/H1302/112.).

DATA COLLECTION

For this analysis we have used four data sources. 1) The hospital maternity records for information on birth weight, gestational age, gender of a child, number of births 2) the community health records for weights at 1 and 3 months. 3) The BiB1000 cohort records for **weights at 6, 12, 18, 24 and 36 months. 4) Information on ethnicity of the mother, smoking by** the mother, educational level for the mother were collected through the baseline questionnaire during recruitment. Age- and Sex-specific standardised weight scores (SDS) were derived according to World Health Organisation growth standards [16] in LMSgrowth Microsoft excel add-in software.[17] In this study, we only included Pakistani and White British as the other ethnicities were very few in number to form groups for comparative analyses. Only singleton term births in the BiB1000 children were included. Therefore, 1364 singleton term children are included in the analysis.

COVARIABLES CONSIDERED:

We adjusted for the following variables that are known to affect the birth weight and growth: mother's ethnicity,[18] maternal smoking during pregnancy and parity,[19] and maternal level of education.[20]

STATISTICAL ANALYSIS AND SOFTWARE

Growth patterns analysis was performed by fitting two growth models in Mplus software version 7.11.[21] First, we fitted an overall and a multi-group Latent Growth Curve Model (LGCM) to estimate overall and ethnic-specific (i.e. Pakistani and White British) mean curves under the assumption of homogeneity of growth patterns in each group of population.[12 21 22] Then we fitted a Growth Mixture Model (GMM) to allow for variability (heterogeneity) in each group of population.[12 13 21]

Missing growth data were estimated using a Full Information Maximum Likelihood (FIML) method in which parameters are estimated using all available observations in the dataset. [23 24]

To deal with the nonlinearity of growth patterns, three modelling options were explored: polynomials, piecewise and free-time score functions.[21 22] For the polynomial function, models were fitted by including quadratic and cubic terms alternatively, i.e., one term at a time. For the piecewise function, models were fitted by creating joints or break points of the mean curves at different time points. In the free-time score function, two time points were fixed and the rest were left to be estimated by the model.

When selecting the best fitting model and optimal number of classes, the Log-likelihood, Akaike Information Criterion [25], Bayesian Information Criterion,[26] Bootstrapping Likelihood Ratio Test [27] and the classification quality or entropy [28] model fit statistics were used in combination.

In our growth mixture models, estimations of parameters were performed in two steps. First, we ran 1-9 class models to identify a model with the optimal number of latent classes. Initially, our parameters of the growth variables (i.e., means, variances, and covariances of weight

Z-scores of birth-36 months) were freely estimated. However, the residual variances of one weight measurement (weight-z-scores at 36 months) became negative. As a remedy to that, the variance of the variable was fixed to zero.[29] There was no dramatic change of other parameter estimates due to fixing of this parameter, i.e., all models converged well afterwards.

Second, after determining the model with the optimal number of classes, we re-ran our growth models by including our covariates using a three-step approach [30 31] in order to estimate the multinomial logistic regression coefficients of the latent classes on the covariates.

In significance testing, 95% was used as a cut-off, i.e., a t-value of greater than |1.96 | is reported as statistically significant throughout.

When comparing the growth patterns of Pakistani and white British children in our latent growth curve models, and the latent classes in our growth mixture model, we use WHO growth standards[16] as a point of reference. In converting weight z-scores into percentiles, we use one-sided normal standard distribution. For example, weight z-scores of -1.64, 0, 1.04, and 1.64 are equivalent to the 5^{th}, 50^{th}, 85^{th} and 95^{th} percentiles respectively.

RESULTS:

There were a total of 1364 singleton, term children with 48.5% males and 51.5% females; 44% of White British and 56% of Pakistani origin, i.e., 602 White British children (293 boys and 309 girls), and 762 Pakistani children (368 boys and 394 girls). The correlation among the repeated weight measurements was between 0.346 and 0.934 (Table S2).

LATENT GROWTH CURVE MODEL

Comparison between the non-linear growth functions:

Comparison of the three modelling techniques showed that a piecewise model with two joints (at 3 months and 12 months) performed better than polynomials and free time score functions (results not shown). The Log-likelihood, Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were all optimal, and the residuals of parameter estimates were the smallest when compared to the polynomials and free time score functions. Therefore, all results presented here are of the piecewise models.

According to an overall (one group) growth model, the BiB1000 children had a significant downward slope (-0.707 SDS) between birth and 3 months, a significant upward slope (0.665 SDS) between 3 and 12 months, and non significant downward slope (-0.012 SDS) between 12 and 36 months of age (Table-1). However, results from the multi-group model showed that the White British children had statistically significant downward and upward trends between birth and 36 months ($Slope_{0-3}$ =-0.881 SDS; $Slope_{3-12}$=0.578 SDS; $Slope_{12-36}$=-0.057 SDS), whereas, the Pakistani children had a statistically significant change of trend between birth and 12 months ($Slope_{0-3}$=-0.709 SDS; $Slope_{3-12}$=0.770 SDS) but a non statistically significant change of trend between 12 and 36 months ($Slope_{12-36}$=0.031 SDS).

Table 1: *Parameter estimates of the overall and multi-group Latent Growth Curve piecewise model*

Model		Parameter*	Estimate		P-value
			value	95% CI	
Overall (one group) model		Intercept	-0.116	(-0.174 , -0.058)	<0.001
		$Slope_{0-3}$	-0.707	(-0.970 , -0.443)	<0.001
		$Slope_{3-12}$	0.665	(0.583 , 0.748)	<0.001
		$Slope_{12-36}$	-0.012	(-0.035 , 0.011)	0.32
Multi-group model	White British	Intercept	0.119	(0.030 , 0.209)	<0.01
		$Slope_{0-3}$	-0.881	(-1.289, -0.473)	<0.001
		$Slope_{3-12}$	0.578	(0.451, 0.705)	<0.001
		$Slope_{12-36}$	-0.057	(-0.086 , -0.028)	<0.001
	Pakistani	Intercept	-0.299	(-0.377, -0.221)	<0.001
		$Slope_{0-3}$	-0.709	(-1.006, -0.412)	<0.001
		$Slope_{3-12}$	0.770	(0.684, 0.857)	<0.001
		$Slope_{12-36}$	0.031	(-0.003 , 0.066)	0.07

* Slope subscripts are age in months.

Results from the multi-group analysis also showed that the two ethnicities had distinct growth curves (figure 1b). According to the estimated latent growth parameter estimates (Table 1), the Pakistani children had a standardised birth weight (i.e. weight-z-score) significantly lower than the White British, -0.299 SDS and 0.119 SDS, respectively. In terms of the rate of growth, the Pakistani children showed lower decelaration between birth and 3 months, but higher acceleration between 3 months and 12 months of age than the White British children. Between 12 and 36 months of age, the Pakistani children accelerated whilst the White British children decelerated significantly.

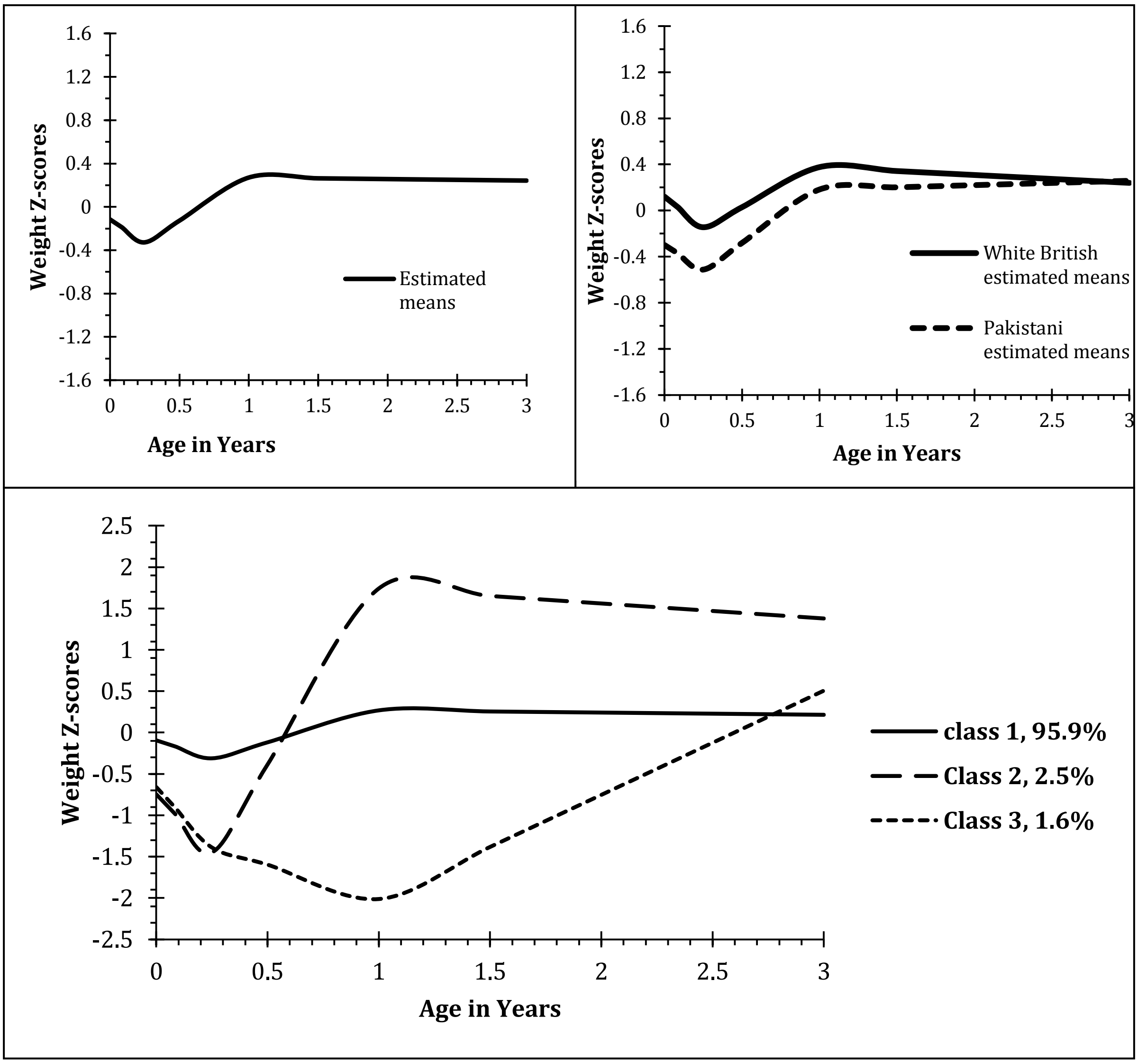

Figure 1: *Estimated mean of standardised weight scores of the overall (a) and multi-group (b) piecewise Latent Growth Curve Models, and three class growth mixture model (c).*

GROWTH MIXTURE MODEL

Determination of optimal class number:

The goodness fit indices for the classification models did not agree (Table-2). However, none of the model fit indices favoured one class (equivalent to the latent growth curve model). While the log-likelihood and AIC favoured the highest class model, the sample size adjusted BIC indicated that the three classes model was optimal. According to simulation studies by Nylund et al [32] and Yang, [33] BIC and sample size adjusted BIC were found to be superior to all Information Criteria indices. Of the two likelihood ratio tests (i.e. Lo-Mendell-Rubin Likelihood Ratio Test (LMR LRT) and Bootstrapped Likelihood Ratio Test (BLRT)), the BLRT was discovered to be superior.[32] In line with the recommendation of these simulation studies, both the adjusted and non adjusted Lo-Mendell-Rubin LRTs rejected the K and K+1 (i.e. K is class number) class models consistently. Our selection of the optimal number of classes was, therefore, guided mainly by sample size adjusted BIC and BLRT values. Due to high computational time needed for BLRT estimation, only 2-5 class models were run and selected for comparison based on ABIC and classification quality (entropy) values of the classes.

Table 2: *Model fit results for selection of optimal number of classes Growth Mixture Model*

Number of latent classes	**Model fit Criterion**				**Classification quality**	**Likelihood ratio test**
	-2LL	AIC	ABIC	df	Entropy	BLRT (-2LL diff; df diff; and P-values)
1 class	11,886.2	11,928.2	11,971.1	21	N/A	N/A
2 classes	11,839.8	11,891.9	11,945.0	26	0.92	46.34; 5; <0.001
3 classes	11,805.4	11,867.5	11,930.7	31	0.91	34.42; 5; 0.002
4 classes	11,786.6	11,858.6	11,932.1	36	0.89	18.80; 5; 0.070
5 classes	11,766.6	11,848.7	11,932.4	41	0.70	19.85; 5; 0.065
6 classes	11,749.6	11,841.5	11,935.4	46	0.70	-
7 classes	11,731.8	11,833.6	11,937.7	51	0.69	-
8 classes	11,716.6	11,828.6	11,942.9	56	0.64	-
9 classes	11,702.6	11,824.6	11,949.2	61	0.66	-

LL= Log-likelihood; AIC=Akaike Information Criterion; ABIC= sample size adjusted Bayesian Information Criterion; BLRT= bootstrapped likelihood ratio test; -2LL diff=2 times the Log-likelihood difference, df=degrees of freedom (number of free parameters); df diff= difference in the degree of freedom.

Based on class numeration results (Table-2) and probability class assignment (Table S3), the BiB1000 children had three optimal classes (Figures 1c & S1). Class 1, which comprised 95.9% of the sample population, were characterised by consistent growth from birth until the age of three (Figure 1c). This group of children had a standardised birth weight (intercept) of -0.095; and, statistically significant downward $slope_{0-3}$ (-0.726 SDS; 95% CI: -0.977, -0.474), upward $slope_{3-12}$ (0.646 SDS; 95% CI: 0.571, 0.721), but not significant downward $Slope_{12-36}$ (-0.022 SDS; 95% CI: -0.047, 0.002) (Table 3). Based on the growth patterns, the group can be classified as 'normal growers'. Generally speaking, the means of the standardised weight scores (i.e. from birth to 36 months of age) of this group of children were within the 38th and 61st percentile range when compared to the WHO child growth charts.[34]

Latent class 2, which comprised 2.5% of the population, had the lowest mean standardised birth weight and showed the fastest growth from three months until 12 months when compared to the other two classes (Figure 1c). The group had an estimated mean standardised birth weight (intercept) of -0.746. Between birth and 3 months, they showed a non-statistically significant drop ($Slope_{0-3}$= -2.344 SDS; 95% CI: -7.975, 3.287), then significant change to an upward trend ($Slope_{3-12}$=3.547 SDS; 95% CI: 2.438, 4.655) between 3 and 12 months, and then a non-significant downward trend ($Slope_{12-36}$ SDS=-0.151; 95% CI: -0.504, 0.202) until the age of 3 years (Table 3). When compared to the WHO growth charts, the group's estimated mean standardised weight at birth was 22nd percentile. Then by the age of three months, the estimated mean was at the 7th percentile, and by the age of one year, it was at the 96th percentile.[34] This group can be categorised as 'fast growers'.

The children in class 3 comprising 1.6% of the population are those who showed a consistent downward trend from birth until 12 months, i.e., $Slope_{0-3}$=-2.434 SDS (95% CI: -5.496, 0.628) and $Slope_{3-12}$=-0.692 SDS (95% CI: -1.790, 0.406). Between 12 and 36 months, they showed a significant upward trend ($Slope_{12-36}$=1.050 SDS; 95% CI: 0.534, 1.565). Subsequently, they consistently gained weight until 3 years of age. When compared with the WHO growth charts, their estimated mean birth weight was just above the 25th percentile. By the age of 12 months, it dropped to the 2nd percentile, and then at the age of 3, their mean sharply increased to 69th percentile.[34] Generally speaking, the group can be categorised as 'slow growers'.

Table 3: *parameter estimates of the latent classes of Growth Mixture Model*

Class/model	Parameter	Estimate		P-value
		value	95% CI	
Class 1 ('Normal growers')	Intercept	-0.095	(-0.164, -0.025)	0.007
	$Slope_{0-3}$	-0.726	(-0.977, -0.474)	<0.001
	$Slope_{3-12}$	0.646	(0.571, 0.721)	<0.001
	$Slope_{12-36}$	-0.022	(-0.047, 0.002)	0.072
Class 2 ('Fast growers')	Intercept	-0.746	(-1.641, 0.149)	0.102
	$Slope_{0-3}$	-2.344	(-7.975, 3.287)	0.415
	$Slope_{3-12}$	3.547	(2.438, 4.655)	<0.001
	$Slope_{12-36}$	-0.151	(-0.504, 0.202)	0.401
Class 3 ('Slow growers')	Intercept	-0.660	(-1.551, 0.230)	0.146
	$Slope_{0-3}$	-2.434	(-5.496, 0.628)	0.119
	$Slope_{3-12}$	-0.692	(-1.790, 0.406)	0.217
	$Slope_{12-36}$	1.050	(0.534, 1.565)	<0.001
Linear regression	Intercept ON Ethnicity	-0.450	(-0.560, -0.340)	<0.001
	$Slope_{0-3}$ ON Ethnicity	0.333	(-0.093, 0.759)	0.126
	$Slope_{3-12}$ ON Ethnicity	0.168	(0.040, 0.296)	0.01
	$Slope_{12-36}$ ON Ethnicity	0.091	(0.046, 0.135)	<0.001

Comparing growth patterns between White British and Pakistani children, the results showed that Pakistani children were lighter by -0.450 SDS (i.e. 190 grams) at birth, and had faster growth between 3 and 36 months than White British children (Table-3). Furthermore, when the probabilities of two ethnicities were compared in their being in the three classes (reference=class 1), the Pakistani children had a higher probability of being in the 'faster growers' and 'slow growers' groups than White British, i.e., ORs of 2.90 (95% CI: 0.91, 9.25) and 15.63 (95% CI: 1.06, 230) for the 'fast growers' and 'slow growers' respectively (Table-4).

Table 4: *Results of categorical latent variable multinomial logistic regressions using 3-step procedure*

Class	covariate	Risk estimate (OR)		P-value
		value	95% CI	
Class 2 (fast growers)[a]	Ethnicity (ref=White British)	2.90	(0.91,9.25)	0.072
	Smoking (ref=yes)	0.23	(0.04, 1.29)	0.095
	Mother's education(ref=5 GSCEs)	1.87	(0.87, 4.01)	0.111
	Parity(ref=Primiparous)	0.30	(0.08, 1.21)	0.092
Class 3 (slow growers)[a]	Ethnicity (ref=White British)	15.63	(1.06, 230)	0.045
	Smoking (ref=yes)	0.15	(0.02, 1.01)	0.051
	Mother's education(ref=5 GSCEs)	1.03	(0.53, 2.01)	0.934
	Parity(ref=Primiparous)	1.42	(0.17,11.88)	0.747

[a] reference is class 1 (the normal growers)

DISCUSSION

In this growth analysis, we have identified that the BiB1000 children had three distinct growth patterns: 'normal growers' (95.9%), 'fast growers' (2.5%) and 'slow growers' (1.6%). The Pakistani children were more likely to be in either the 'fast' or 'slow growers' group than the White British. Our results also showed that Pakistani children are lighter than the White British by 190 grams at birth. Although there was no difference in the change of weight in the first three months, Pakistani children showed faster growth than the White British between 3 and 36 months of age.

From our results, we observed that both the Pakistani and white British children tended to consistently growth slowly until 3 months of age when compared to the WHO growth standards (Figures 1a & 1b). The WHO growth standards population was made up of healthy breastfed children whose mothers were breastfeeding and not smoking. [16] Therefore, it can be speculated that the slow growth observed in our study population was probably due to difference in life-style and child feeding habits of mothers.

We also noted that our abnormal grower groups (fast and slow growers) have similarities with the growth trajectories shown by Eriksson et al [1] that also reported low birthweight coupled with fast catch-up growth is associated with adulthood hypertension, although the authors did not use WHO growth standards as a reference. However, a study by Rzehak et al [7] that used the same standardization method as ours has reported that children who persistently grew faster as compared to those grew consistently normal have an increased risk of asthma by 30%.

The group that has been identified by our model as the 'fast growers' is also composed of those children observed to be overweight until three years (Figure 1c). In contrast to a previous systematic review and meta-analysis that reported a significant associated risk of overweight with maternal smoking,[35] our finding was not statistically significant (Table 4). We have found no statistically significant associated risk of overweight (or being in the 'fast growers' group) with maternal education (as a proxy for Socio-economic Status), parity and ethnicity.

The results of our LGCM are in agreement with a previous report on BiB1000 children.[10] However, our model fit statistics indicated that the LGCM, which is equivalent to multi-level spline models, was not robust. Moreover, our model fit statistics values in the determination of a model with optimal number of classes showed that a model with three classes was more parsimonious than a model with one class. In other words, the GMM fitted the data better than the LGCM.

Latent Growth Curve and multi-level spline models which both assume that all individuals in a group have homogenous growth patterns [13 36] and ignore the variability among individuals [9] are restrictive. Despite the fact that these modeling techniques can provide information on the variation of growth patterns between a predefined groups, [37] they do not allow us to test if there are more than one growth pattern within the predefined groups and/or the whole population. When investigating disease aetiology, it can be argued that it is the difference in growth patterns in the life-course that is of primary interest rather than the ethnic origin of a child. With this in mind, it would be useful to initially characterise the growth patterns of a population (i.e. estimating growth trajectories) then investigate ethnicity or whether any variable has any influence on the growth trajectories. Alternatively, one can group the study population (e.g. by ethnicity) first, then test if there are more than one growth trajectories within the group. Here, the Growth Mixture Modelling allows us to capture information where individuals in a group or population are allowed to have different growth patterns.[36]

The choice between multi-level spline and growth mixture modelling depends mainly on the depth of information that one wants to derive from the data and the number of repeated measurement points. Growth mixture modelling provides extra information (e.g. distinct growth trajectories) about the study population. However, if the repeated measurement points are too many, parameter estimations using GMM can have more convergence problems than the multi-level spline models. In addition to that, it can be the case that the number of optimal classes and growth trajectories generated by the GMM do not agree with the initial hypothesis where a researcher may opt for the most interpretable number of classes despite the model identifies different number of optimal classes. Therefore, there is a trade-off when choosing between the two modelling techniques.

Our study has weakness and readers should interpret our results cautiously. Firstly, the proportion of missing data was high in some follow up ages (Table S2) due to absence of children during visits and the fact that some registered weight measurements did not reflect the actual follow up age of the children, although we have implemented missing data modeling techniques to address the problem. Secondly, participation in the BiB1000 cohort children depended on consent of mothers—recruitment was not random. Hence, study participants may not be representative of the Bradford population. Thirdly, our GMM has identified three classes that the proportions of children in the 'fast' and 'slow' grower groups were only 2.5% and 1.6% respectively. This would mean that the evidence that the three classes differ in terms of risks of association may become less robust.

The strength of our growth analysis is threefold. First, we used repeated measurements and a more advanced analytic technique (i.e. latent growth modelling) to analyse life-course growth trajectories. Second, we were able to apply FIML missing data modeling technique to minimise parameter estimate biases as compared to list-wise and pair-wise deletion methods under missing data at random assumptions.[24 38] Third, we are also able to use age- and sex-specific standardised weight scores which have the advantage of clearly depicting the growth patterns of children in comparison to the standard growth reference[16]. The standard scores are convertible to percentiles[17] which enable us to draw clear conclusions about the study population.

In conclusion, we have confirmed that Pakistani children are lighter at birth and have faster growth than White British children. More importantly, we have described three distinct growth patterns in this childhood population. These growth patterns may provide better insight in predicting the risk of childhood or early adulthood diseases in life-course research.

Acknowledgments: Born in Bradford is only possible because of the enthusiasm and commitment of the Children and Parents in BiB. We are grateful to all the participants, health professionals and researchers who have made Born in Bradford happen.

Funding: TF Mebrahtu is funded by the Hall Dorman Research PhD Studentship. This paper presents independent research funded by the National Institute for Health Research (NIHR) under the Collaborations for Leadership in Applied Health Research and Care (CLAHRC) programme for Leeds, York and Bradford and the Programme Grants for Applied Research funding scheme (RP-PG-0407-10044). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Contributors: TF Mebrahtu, RG Feltbower and RC Parslow conceived the idea. TF Mebrahtu designed the statistical approach and performed the analyses. RG Feltbower and RC Parslow supervised the design of the statistical approach and analyses. TF Mebrahtu produced the draft of the manuscript. RG Feltbower, RC Parslow and ES Petherick revised and commented on the manuscript. TF Mebrahtu finalised the manuscript. ES Petherick provided the data and advice on its interpretation.

Competing interests: none declared.

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