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Application of multilevel linear spline models for analysis of growth trajectories in a cohort with repeat antenatal and postnatal measures of growth: a prospective cohort study

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ABSTRACT

Objectives To model trajectories of antenatal and postnatal growth using linear spline multilevel models.

Design Prospective cohort study.

Setting Maternity hospital in Dublin, Ireland.

Participants 720–759 mother–child pairs from the ROLO study (initially a randomised control trial of a low glycaemic index diet in pregnancy to prevent recurrence of macrosomia [birth weight >4 kg]).

Primary outcomes Trajectories of growth from 20 weeks gestation (abdominal circumference [AC], head circumference [HC] and weight) or birth (length/height) to 5 years.

Results Over 50% of women had third-level education and 90% were of white ethnicity. Women were a mean (SD) age of 32 years (4.2) at recruitment. The best fitting model for AC, HC and weight included a model with 5 linear spline periods. The best fitting models for length/height included a model with 3 linear spline periods from birth to 6 months, 6 months to 2 years and 2 years to 5 years. Comparison of observed and predicted values for each model demonstrated good model fit. For all growth measures, growth rates were generally fastest in pregnancy or immediately post partum (for length/height), with rates of growth slowing after birth and becoming slower still as infancy and childhood progressed.

Conclusion We demonstrate the application of multilevel linear spline models for examining growth trajectories when both antenatal and postnatal measures of growth are available. The approach may be useful for cohort studies or randomised control trials with repeat prospective assessments of growth.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Using prospective follow up of a randomised control trial of predominantly macrocsomic infants, trajectories of antenatal and postnatal growth up to age 5 years were modelled as a single trajectory.
⇒ The linear spline multilevel modelling method used maximises sample sizes for analyses, reduces selection bias and produces more precise standard errors compared with single-level approaches.
⇒ We were not able to explore non-linear growth due to the sparsity of repeated measures and this cohort is unlikely to represent the growth rates of a general population since their development is above average due to the high prevalence of macrosomia.

INTRODUCTION

Antenatal and childhood growth are important indicators of fetal and child health and development and are associated with health in adult life.[1 2] Consequently, modelling of growth trajectories, identifying causes and predictors of different growth trajectories and relating growth trajectories in the early life course to later life health is important for informing a life course approach to disease prevention.[3–5]

A key aspect of understanding growth patterns, their causes, predictors and outcomes includes appropriate modelling of longitudinal growth data.[3] Since repeated measures of growth within individuals are not independent of each other and the scale and variance of growth measures often changes over time, traditional approaches to analysis of growth data, such as single-level multiple regression, do not take account of the clustering of repeated measures within individuals.[3] Moreover, the true shape of growth over time cannot be modelled using such approaches. While appropriate methods for the study of longitudinal growth data have been applied to antenatal and childhood growth measures in many cohort studies, most studies to date have examined antenatal growth[6 7] or postnatal growth as separate processes/trajectories.[8–14] Appropriate modelling of growth data as a continuum from antenatal to postnatal life is important to accurately characterise the shape of growth

Table 1 N repeated measures included in analyses for each growth measure

	20 weeks	34 weeks	Birth	6 months	2 years	5 years
Abdominal circumference	656	732	265	280	336	385
Head circumference	656	700	634	280	333	386
Weight	655	730	756	280	339	387
Length/height			634	280	339	386

from early gestation into childhood to better understand it's aetiology. In addition, it also enables such trajectories to be examined as outcomes for preconception or early pregnancy exposures or to be examined themselves as exposures for later health outcomes.[3]

Using data from the prospective follow up of the Randomised cOntrol Trial of LOw glycaemic diet in pregnancy (ROLO) study, we demonstrate the application of linear spline multilevel models for modelling antenatal and postnatal growth trajectories using 4 measures of anthropometry (abdominal circumference [AC], head circumference [HC], weight and length/height) from 20 weeks' gestation to age 5 years.

METHODS

Study population

The ROLO study is a randomised control trial of a low glycaemic index diet in pregnancy that recruited 800 secundigravid women who had previously given birth to a baby weighing over 4 kg between 2007 and 2011 at the National Maternity Hospital, Dublin, Ireland.[15] Women were recruited at first antenatal consultation. Women with any underlying medical disorders, including a history of gestational diabetes, those on any drugs, those unable to give full informed consent, aged less than 18 years, of gestation greater than 18 weeks, and having multiple pregnancies were excluded. Women were randomised to either the intervention group which received dietary advice on a low glycaemic diet, or the control group who received routine antenatal care.

PATIENT AND PUBLIC INVOLVEMENT

None.

Measurement of anthropometry

Antenatal measures

Fetal measurements were obtained from ultrasound scans performed on mothers at medians of 20+6 (IQR 20+1–21+5) and 34+1 (IQR: 33+5–34+5) weeks' gestation, including AC and HC. An estimated fetal weight at 20 and 34 weeks' gestation was calculated using the Hadlock 4-parameter formula. Ultrasound measurements were taken by 2 ultrasonographers using a Voluson 730 Expert (GE Medical Systems, Germany) using standard procedures.

Postnatal measures

At delivery, infants' AC, HC, weight and length were recorded. Follow-up anthropometry assessments were also obtained in childhood at 6 months, 2 years and 5 years.[15–17] All measurements were obtained and calculated by a trained member of the research team. At 6 months, 2 years and 5 years, weight (kg) of the child was measured using a calibrated stand on digital weighing scale (SECA 813) to the nearest 0.1 kg by a trained research team member. Children were measured in light clothing without shoes. Standing height was measured, without shoes, with head aligned in the Frankfort plain, using a free-standing stadiometer (SECA 217) and measurements recorded to the nearest 0.1 cm. The child's HC and AC were measured using a SECA ergonomic circumference measuring tape, to the nearest 0.1 cm. All measurements were recorded 3 times and the average calculated to improve reliability.

Statistical analysis

We used multilevel models to examine trajectories of change in AC, HC, weight and length/height from 20 weeks gestation to age 5 years.[18 19] Multilevel models (MLMs) estimate mean trajectories of the outcome while accounting for the non-independence (ie, clustering) of repeated measurements within individuals, change in scale and variance of measures over time and differences in the number and timing of measurements between individuals (using all available data from all eligible participants under a missing at random [MAR] assumption).[3 20] Table 1 shows the measures available at each occasion, demonstrating differences in the number of measurements available between individuals over time. The MLM approach used here, therefore, was advantageous as it allowed us to include data from all participants, regardless of whether they had 1 or multiple measures as shown in table 1.

Change in all 4 growth measures was estimated here using linear spline multilevel models (2 levels: measurement occasion and individual).[3] Linear splines allow knot points to be fit at different ages to derive periods in which change is approximately linear. The optimal linear spline model for each growth measure was selected by examining observed data for each growth measure and comparing model fit statistics of different models. Model fit statistics examined included Akaike's information criterion and observed and predicted values of each growth measure across the age range of the model. For AC, HC and weight, we compared the following models;

models that assumed linear change over time, models with knots placed at birth and 5 years only (2 spline periods), models with knots placed at birth, 2 years and 5 years (3 spline periods), models with knots placed at birth, 6 months, 2 years and 5 years (4 spline periods) and finally a model which knots at 34 weeks, birth, 6 months, 2 years and 5 years. The best fitting model for these included a model with knots at each measurement occasion giving rise to 5 linear spline periods from 20 weeks' to 34 weeks' gestation, 34 weeks' gestation to birth, birth to 6 months, 6 months to 2 years and 2 years to 5 years. For length/height, we compared the following models; a model which assumed linear change over time, a model with knots at 2 and 5 years only (2 spline periods) and a model with knots at 6 months, 2 years and 5 years (3 spline periods). The best fitting model for length/height included a model with 3 linear spline periods from birth to 6 months, 6 months to 2 years and 2 years to 5 years.

All outcomes were normally distributed at each measurement occasion. Except for length/height which did not include antenatal measures, trajectories were centred on the first available measure (20 weeks gestation) for AC, HC and weight. Length/height trajectories were centred at birth. For all models, we placed no restrictions on the variance–covariance matrices of level 2 (individual level) random effects. Given the substantial change in scale and variance of growth from antenatal to postnatal life, we also aimed to allow occasion level measurement error to vary with age (level 1 random effects for the slope). Therefore, all models included a level 1 random effect for the slope while the HC model also included a level 1 random effect for the intercept. The final models for AC, HC and weight trajectories from 20 weeks gestation each took the following form: growth trajectory$_{ij}$= β_0 + u_{0j} + (β_1+ u_{1j})s_{ij1} + (β_2+ u_{2j})s_{ij2} + (β_3 + u_{3j})s_{ij3} + (β_4 + u_{4j}) s_{ij4} + (β_5 + u_{5j})s_{ij5}+e_{ij} where for person j at measurement occasion i; β_0 represents the fixed effect coefficient for the average intercept, β_1–β_5 represent fixed effect coefficients for the average linear slopes of each linear spline, u_{0j}–u_{5j} indicate person-specific random effects for the intercept and slopes, respectively, and e_{ij} represents the occasion-specific residuals or measurement error which were allowed to vary with age. The final model for length took a similar form but with only 3 linear spline periods due to the absence of measures prior to birth. Code for the application of these models using the 'runmlwin' command from MlWin[21] within Stata V.16[22] is included in online supplemental material.

Table 2 Characteristics of ROLO participants included in the analysis of length/height, by sex

	Male N=358	Female N=362
	n (%)	n (%)
Completed third-level education	151 (50.3)	187 (60.9)
Non-white ethnicity	5 (1.4)	9 (2.5)
	Mean (SD)	**Mean (SD)**
Mothers age at delivery (years)	32.3 (4.2)	32.6 (4.2)
Pobal HP index (unit)	5.3 (10.8)	5.4 (9.7)
Mothers BMI (kg/m^2)	27.1 (5.2)	26.2 (4.4)
Birth weight (kg)	4.1 (0.5)	4.0 (0.4)
	Median (IQR)	**Median (IQR)**
Gestational age at delivery (weeks)	40.4 (39.6–41.1)	40.3 (39.6–41.1)

The Pobal HP index is a census-based deprivation index for the Republic of Ireland which has a mean of 0 (SD=10) in the general population and ranges from −39 (most deprived) to 40 (most affluent).
BMI, body mass index; HP, Haase and Pratschke; ROLO, Randomised cOntrol Trial of LOw glycaemic diet in pregnancy.

RESULTS

A total of 754, 756 and 759 offspring were included in analyses of AC, HC and weight, respectively, while 720 offspring were included in analyses of length/height. Table 1 includes the number of measures of each growth measure at each measurement occasion with number of measures available broadly similar across growth measures; for example, weight measures available on each occasion included 655 measures at 20 weeks gestation, 730 at 34 weeks gestation, 756 at birth, 280 at 6 months, 339 at 2 years and 387 at 5 years.

Of participants included in analyses (table 2), over 50% had completed third-level education and a majority (>90%) were of white ethnicity. Among mothers of male babies, mean age (SD) at delivery was approximately 32.3 (4.2) years, mean (SD) BMI at delivery was 27.1 (5.2) kg/m^2, mean (SD) birth weight at delivery was 4.1 (0.5) kg and median (IQR) gestational age was 40.4 (39.6, 41.1) weeks. Mothers of male babies had relatively low levels of deprivation as indicated by the mean (SD) Pobal HP (Haase and Pratschke) index of 5.3 (10.8) (note the Pobal HP index is a census-based deprivation index in Ireland which has a mean of 0 (SD=10) in the general population and ranges from −39 [most deprived] to 40 [most affluent])[23] Characteristics were broadly similar for mothers of female babies though mothers of female babies had somewhat higher levels of third-level education (~60%). Model fit as judged by differences between observed growth measures and those predicted by the models for AC, HC, weight and length are shown in tables 3–6. Overall, our models have good fit as all reference ranges for the difference between observed and predicted are less than the SD of the observed or less than 10% of the observed value which can be used as a rule of thumb for the assessment of model fit.

Trajectories of AC, HC and weight from 20 weeks' gestation to 5 years and trajectories of length/height from birth to 5 years by intervention status and sex are shown in tables 7 and 8 and figures 1–4). AC and HC had the fastest

Table 3 Model details for abdominal circumference

	Total no of observations	Mean observed (SD) in cm	Mean predicted (SD) in cm	Mean difference (observed—predicted) in cm	95% level of agreement between observed and predicted in cm
20 weeks to 34 wks	531	22.48 (6.92)	22.59 (6.86)	−0.08	−1.13 to 0.97
34 weeks to birth	517	32.22 (2.08)	32.35 (1.19)	0.08	−2.01 to 2.17
Birth to 6 months	315	38.21 (5.93)	36.01 (4.51)	−0.05	−3.64 to 3.53
6 months to 2 years	272	47.91 (5.37)	47.84 (3.96)	0.09	−4.25 to 4.42
2 years to 5 years	681	50.25 (8.98)	54.03 (2.72)	−0.06	−6.11 to 6.00

Model fit is summarised for age periods rather than specific ages as there may not be enough people at specific ages to provide a meaningful summary.

Table 4 Model details for head circumference

	Total no of observations	Mean observed (SD) in cm	Mean predicted (SD) in cm	Mean difference (observed—predicted) in cm	95% level of agreement between observed and predicted in cm
20 weeks to 34 weeks	292	22.90 (4.87)	22.86 (4.83)	0.09	−0.55 to 0.73
34 weeks to birth	680	32.54 (1.67)	32.63 (1.53)	−0.01	−0.61 to 0.59
Birth to 6 months	642	37.57 (3.70)	37.39 (3.46)	0.00	−0.48 to 0.47
6 months to 2 years	274	47.29 (2.98)	47.28 (2.87)	0.01	−0.47 to 0.49
2 years to 5 years	661	48.89 (6.16)	51.18 (1.64)	−0.01	−0.75 to 0.73

Model fit is summarised for age periods rather than specific ages as there may not be enough people at specific ages to provide a meaningful summary.

Table 5 Model details for weight

	Total no of observations	Mean observed (SD) in kg	Mean predicted (SD) in kg	Mean difference (observed—predicted) in kg	95% level of agreement between observed and predicted in kg
20 weeks to 34 weeks	294	0.97 (0.81)	1.04 (0.77)	−0.07	−0.24 to 0.10
34 weeks to birth	708	2.93 (0.58)	2.89 (0.51)	0.04	−0.31 to 0.38
Birth to 6 months	735	4.87 (1.87)	4.88 (1.81)	−0.01	−0.44 to 0.43
6 months to 2 years	276	10.92 (2.59)	10.91 (2.53)	0.01	−0.36 to 0.38
2 years to 5 years	695	15.54 (6.60)	18.30 (3.88)	−0.01	−0.42 to 0.41

Model fit is summarised for age periods rather than specific ages as there may not be enough people at specific ages to provide a meaningful summary.

rates (table 7) of growth from 20 to 34 weeks' gestation with growth rates continuing to slow thereafter up to age 5 years. Weight had the fastest growth rate from 34 weeks' gestation to birth with growth rates slowing somewhat from birth to 6 months and continuing to slow thereafter until 5 years. Length/height had the fastest growth rates from birth to 2 years, with the growth rate decreasing thereafter and slowing further from 2 to 5 years.

We found no strong evidence of differences in trajectories of AC, weight and length/height between the intervention and control group, but we found some evidence of slightly greater HC (difference 0.27 cm (95% CI 0.03 to 0.51) emerging among the control group at 5 years (table 8). AC trajectories did not differ between males and females, though we found some evidence of modest differences in HC, weight and length/height trajectories between males and females. Females had lower HC at 20 weeks gestation with this difference widening at birth and persisting at age 5 years (difference at 5 years: −0.91 cm, 95% CI −1.14 to −0.68). Females had −0.15 kg (95% CI −0.21 to −0.08) lower birth weight and slower postnatal growth rates in weight leading to −0.50 kg (95% CI −0.96 to −0.05) lower weight among females at 5 years. Similarly, females were −0.83 cm (95% CI −1.17 to −0.48) shorter in length at birth and had slower postnatal growth rates in length/height leading to −1.22 cm

Table 6 Model details for length

	Total no of observations	Mean observed (SD) in cm	Mean predicted (SD) in cm	Mean difference (observed—predicted) in cm	95% level of agreement between observed and predicted in cm
Birth to 6 months	475	57.55 (7.51)	57.14 (7.25)	0.0001	−0.03 to 0.03
6 months to 2 years	304	81.03 (10.12)	81.03 (10.08)	−0.002	−0.57 to 0.56
2 years to 5 years	574	104.07 (12.24)	106.42 (9.79)	0.0004	−2.92 to 2.92

Model fit is summarised for age periods rather than specific ages as there may not be enough people at specific ages to provide a meaningful summary.

Table 7 Mean growth rates of anthropometry and mean difference in growth rates by intervention status and sex in the ROLO cohort from 20 weeks to 5 years

	Mean growth rate (95% CI) in intervention	Mean growth rate difference (95% CI) in controls compared with intervention	Mean growth rate (95% CI) in males	Mean difference in growth rate (95% CI) in females compared with males
Abdominal circumference				
20 weeks to 34 weeks (cm/week)	1.20 (1.18 to 1.22)	0.01 (–0.02 to 0.03)	1.20 (1.19 to 1.22)	0.002 (–0.02 to 0.03)
34 weeks to birth (cm/week)	0.26 (0.19 to 0.33)	0.03 (–0.07 to 0.13)	0.28 (0.21 to 0.35)	–0.01 (–0.11 to 0.09)
Birth to 6 months (cm/week)	0.40 (0.37 to 0.43)	–0.01 (–0.05 to 0.03)	0.41 (0.38 to 0.44)	–0.03 (–0.06 to 0.01)
6 months to 2 years (cm/week)	0.08 (0.07 to 0.09)	–0.001 (–0.01 to 0.01)	0.07 (0.06 to 0.08)	0.02 (0.004 to 0.03)
2 years to 5 years (cm/week)	0.03 (0.02 to 0.03)	–0.0002 (–0.01 to 0.01)	0.03 (0.02 to 0.03)	–0.002 (–0.01 to 0.01)
Head circumference				
20 weeks to 34 wks (cm/week)	1.01 (1.00 to 1.02)	–0.002 (–0.02 to 0.01)	1.02 (1.01 to 1.03)	–0.01 (–0.02 to 0.004)
34 weeks to birth (cm/week)	0.64 (0.61 to 0.67)	0.05 (0.004 to 0.09)	0.69 (0.66 to 0.72)	–0.06 (–0.10 to –0.01)
Birth to 6 months (cm/week)	0.33 (0.32 to 0.35)	–0.01 (–0.03 to 0.003)	0.34 (0.33 to 0.35)	–0.03 (–0.04 to –0.01)
6 months to 2 years (cm/week)	0.06 (0.05 to 0.06)	0.004 (–0.001 to 0.01)	0.06 (0.05 to 0.06)	0.005 (–0.0003 to 0.009)
2 years to 5 years (cm/week)	0.01 (0.01 to 0.01)	0.001 (–0.001 to 0.003)	0.01 (0.01 to 0.01)	0.001 (–0.001 to 0.003)
Weight				
20 weeks to 34 wks (kg/week)	0.16 (0.16 to 0.17)	–0.002 (–0.01 to 0.001)	0.16 (0.16 to 0.17)	–0.002 (–0.01 to 0.002)
34 weeks to birth (kg/week)	0.24 (0.24 to 0.25)	0.01 (–0.003 to 0.02)	0.26 (0.25 to 0.26)	–0.02 (–0.03 to –0.01)
Birth to 6 months (kg/week)	0.17 (0.17 to 0.18)	–0.01 (–0.02 to –0.001)	0.18 (0.17 to 0.19)	–0.02 (–0.04 to –0.01)
6 months to 2 years (kg/week)	0.05 (0.05 to 0.06)	0.005 (0.001 to 0.01)	0.05 (0.05 to 0.06)	0.004 (–0.0004 to 0.009)
2 years to 5 years (kg/week)	0.04 (0.04 to 0.05)	0.0004 (–0.002 to 0.003)	0.04 (0.04 to 0.05)	–0.0003 (–0.002 to 0.002)
Length/height				
Birth to 6 months (cm/week)	0.66 (0.64 to 0.68)	–0.02 (–0.04 to 0.01)	0.68 (0.66 to 0.70)	–0.06 (–0.08 to –0.03)
6 months to 2 years (cm/week)	0.24 (0.24 to 0.25)	0.01 (0.001 to 0.02)	0.24 (0.23 to 0.25)	0.01 (0.01 to 0.02)
2 years to 5 years (cm/week)	0.13 (0.13 to 0.14)	0.0003 (–0.004 to 0.005)	0.13 (0.13 to 0.14)	–0.0003 (–0.005 to 0.004)

ROLO, Randomised cOntrol Trial of LOw glycaemic diet in pregnancy.

Table 8 Mean absolute growth measure and difference in absolute growth measure by intervention status and sex in the ROLO cohort at 20 weeks gestation, birth and 5 years

	Mean (95% CI) in intervention	Mean difference (95% CI) in controls compared with intervention	Mean (95% CI) in males	Mean difference (95% CI) in females compared with males
Abdominal circumference				
20 weeks (cm)	15.96 (15.85 to 16.07)	–0.02 (–0.17 to 0.14)	16.05 (15.94 to 16.16)	–0.20 (–0.35 to –0.04)
Birth (cm)	34.31 (33.94 to 34.68)	0.26 (–0.26 to 0.77)	34.55 (34.18 to 34.93)	–0.22 (–0.74 to 0.29)
5 years (cm)	55.46 (54.91 to 56.02)	–0.03 (–0.82 to 0.76)	55.33 (54.76 to 55.90)	0.23 (–0.57 to 1.02)
Head circumference				
20 weeks (cm)	18.60 (18.52 to 18.68)	–0.11 (–0.22 to 0.01)	18.68 (18.60 to 18.76)	–0.27 (–0.38 to –0.16)
Birth (cm)	36.62 (36.46 to 36.78)	0.14 (–0.08 to 0.37)	37.07 (36.91 to 37.22)	–0.75 (–0.97 to –0.53)
5 years (cm)	51.91 (51.74 to 52.08)	0.27 (0.03 to 0.51)	52.50 (52.33 to 52.67)	–0.91 (–1.14 to –0.68)
Weight				
20 weeks (kg)	0.40 (0.39 to 0.42)	0.002 (–0.02 to 0.02)	0.41 (0.39 to 0.42)	0.002 (–0.02 to 0.02)
Birth (kg)	4.16 (4.11 to 4.21)	0.01 (–0.06 to 0.08)	4.24 (4.19 to 4.28)	–0.15 (–0.21 to –0.08)
5 years (kg)	19.75 (19.43 to 20.08)	0.15 (–0.31 to 0.61)	20.08 (19.75 to 20.41)	–0.50 (–0.96 to –0.05)
Length/height				
Birth (cm)	52.81 (52.56 to 53.06)	–0.13 (–0.48 to 0.22)	53.16 (52.91 to 53.40)	–0.83 (–1.17 to –0.48)
5 years (cm)	109.72 (109.17 to 110.28)	0.25 (–0.54 to 1.04)	110.46 (109.90 to 111.03)	–1.22 (–2.01 to –0.43)

ROLO, Randomised cOntrol Trial of LOw glycaemic diet in pregnancy.

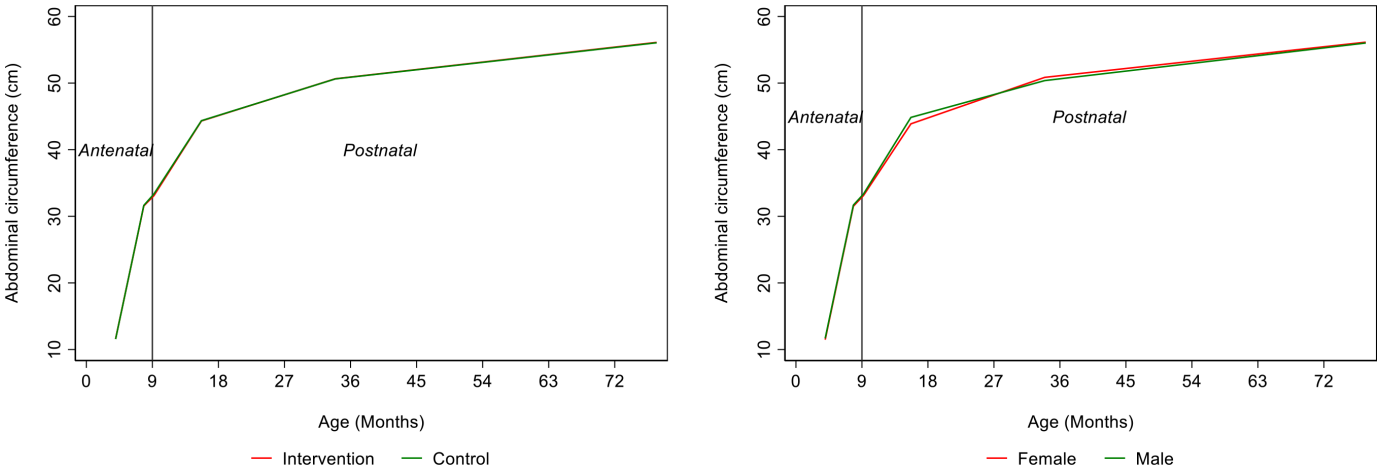

Figure 1 Trajectories of abdominal circumference from 20 weeks gestation to age 5 years by intervention status and sex. Note that X axis displays time in months because trajectory spans the antenatal and postnatal period.

(95% CI −2.01 to −0.43) shorter height among females at 5 years.

DISCUSSION

In this prospective follow up of a randomised control trial of approximately 750 predominantly macrosomic infants, we demonstrated the use of linear spline multilevel modelling to examine trajectories of AC, HC, weight and length/height from 20 weeks' gestation to age 5 years. We showed their applicability to data with repeated measures of growth which span the antenatal and postnatal period, even when as few as 4 repeat assessments are available (in the case of length/height) and measures are sparse.

All women in this study previously had a macrosomic infant, and over half of infants had a birth weight in the macrosomic range (>4 kg). To our knowledge, previous analyses have not examined antenatal and postnatal growth trajectories together. Other cohorts have examined the antenatal or postnatal trajectories of infants like ours,[24 25] but differences in methodological approaches such as the use of a group-based approach in the LIFECODES cohort make comparisons challenging.[25] Our findings for antenatal growth are, however, broadly similar to a study examining the growth trajectories of AC in macrosomic infants from 20 weeks gestation to birth in 244 singleton pregnancies.[26] For example, the macrosomic infants of mothers with gestational diabetes had a fetal AC of approximately 1.3 cm at 20 weeks, increasing linearly leading to an AC of 3.6 cm at birth, which is broadly comparable with the growth rates for AC found in our study. In comparison with findings from analyses of growth in the Avon Longitudinal Study of Parents and Children (ALSPAC), Born in Bradford, Generation XXI, Pelotas and PROBIT cohorts,[3] our postnatal growth rates are expectedly slower than the growth rates of these general population cohorts. This is consistent with the 'catch-down' or slower postnatal growth expected in our high birth weight cohort.[27] For example, infants in our cohort were born 52.8 cm in length and grew at 2.85 cm per month in the first 3 months after birth; this growth rate is slower than that of infants in the ALSPAC cohort, born

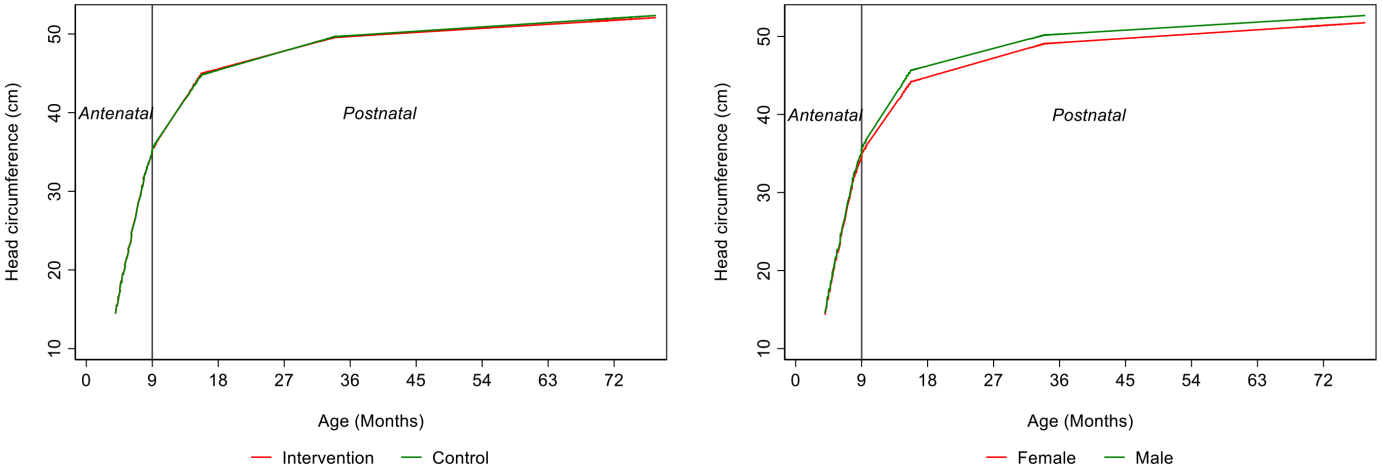

Figure 2 Trajectories of head circumference from 20 weeks gestation to age 5 years by intervention status and sex. Note that x-axis displays time in months because trajectory spans the antenatal and postnatal period.

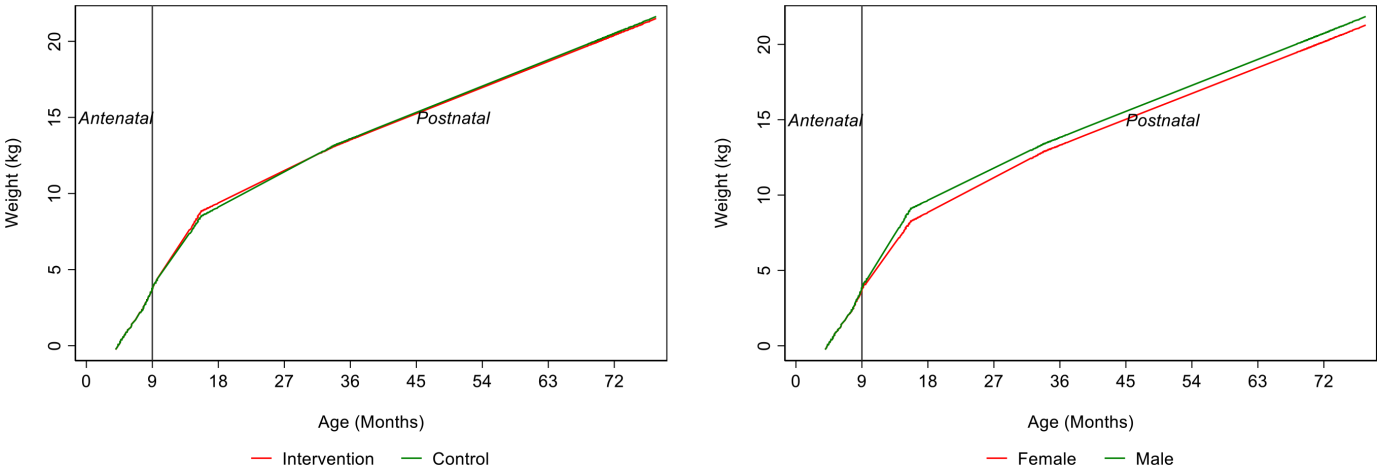

Figure 3 Trajectories of weight from 20 weeks gestation to age 5 years by intervention status and sex. Note that x- axis displays time in months because trajectory spans the antenatal and postnatal period.

50 cm in length and growing at the faster rate of 3.57 cm per month in the 3 months after birth. Our growth rates are more comparable to those of the PROBIT cohort which included only infants greater than 2500 g birth weight and is the cohort in this analysis likely to be most similar to ours (birth length 51.4 cm and growth rate of 2.96 cm per month in the 3 months after birth). However, comparisons with previous studies should be undertaken with caution due to population differences (high birth weight vs general populations) and differences in methodological approaches.

There are several strengths to the general approach of multilevel models taken here; these include the ability to maximise sample sizes for analyses and reduce selection bias compared with single-level approaches since multilevel models can include all participants with at least 1 growth measure under an MAR assumption.[3] This is particularly advantageous where attrition rates from cohorts are high. Further advantages include more precise standard errors which consider the non-independence of repeated measures. There are also additional advantages to the approach of modelling antenatal and postnatal growth together in our cohort. A practical advantage includes the ability to examine this trajectory as a single trajectory outcome for prepregnancy or gestational exposures, thereby providing insights into the timing of the impact of exposures during pregnancy that analyses of summary birth anthropometry measures alone (such as birth weight) cannot provide. Moreover, because the associations of prepregnancy or gestational exposures can be examined with antenatal and postnatal growth rates in a single model it is possible to gain insights into whether associations have intrauterine mechanisms, intrauterine and postnatal mechanisms or perhaps intrauterine mechanisms that persist in postnatal life. Importantly, this latter finding would be overlooked entirely in a model which examines postnatal growth trajectories alone. In addition, the modelling of antenatal and postnatal growth together allows participants with only 1 antenatal measure and no postnatal measure or vice versa to be included in analyses, with a full trajectory estimated for that participant under the previously discussed MAR assumption.

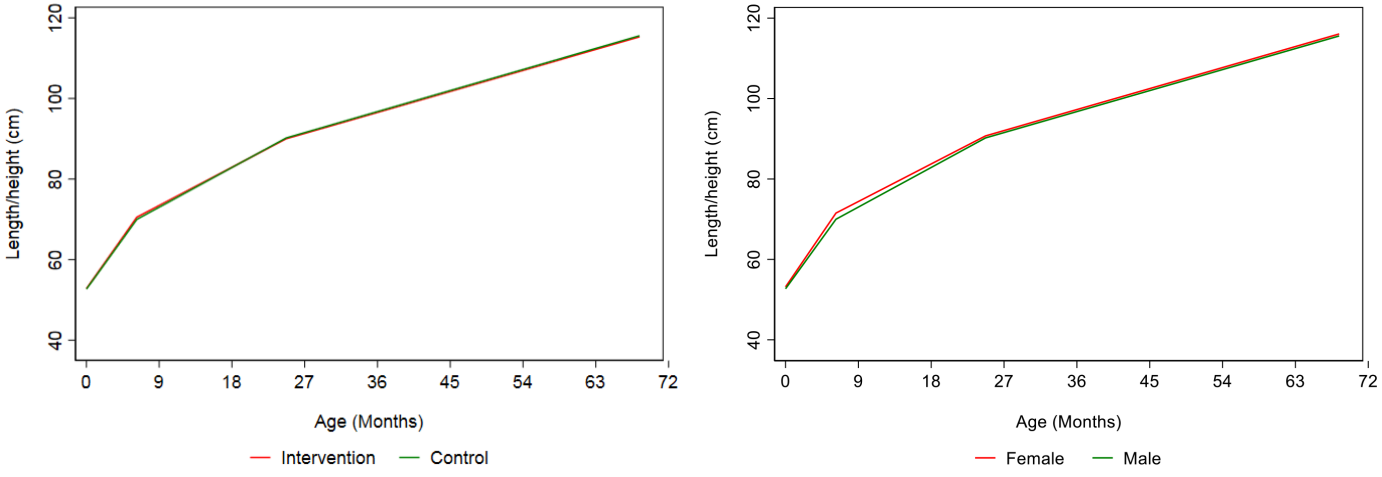

Figure 4 Trajectories of length/height from birth to age 5 years by intervention status and sex. Note that x-axis displays time in months.

This can boost sample sizes[28] and reduce selection bias induced by analysing antenatal and postnatal trajectories separately because participants with no antenatal or no postnatal measure would be excluded from their respective trajectory analyses whereas in the joint-modelling approach a full trajectory (from antenatal to postnatal life) can be estimated for these participants. Limitations of this work include an inability to explore other non-linear growth patterns such as fractional polynomials due to the sparsity of measures which did not allow a range of possible shapes of growth trajectories to be explored.[3] In cohorts with greater numbers of repeated measures and density of repeats, linear spline multilevel modelling can be implemented and compared with other possible shapes include fractional polynomials which have been shown to provide a more biologically intuitive shape of change.[3] However, the linear spline approach demonstrated here provides many practical advantages including being more easily interpretable, allowing analysts to split trajectories into distinct periods of change that can then be easily related to exposures and outcomes. It should be noted that this cohort are unlikely to represent the growth rates or trajectories of a general population since their development is above average compared with what would be expected from an age-and gender-matched general population (the cohort is roughly approximated to the 75th centile based on a crude comparison of means and SDs on the UK-WHO [Ireland] chart).[29]

CONCLUSION

We demonstrate the application of multilevel linear spline models for examining growth trajectories when both antenatal and postnatal measures of growth are available. The approach may be useful for cohort studies or randomised control trials with repeat prospective assessments of growth spanning pregnancy and childhood.

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Patient consent for publication Consent obtained directly from patient(s).

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Supplementary Material

Sample code for implementing linear spline multilevel models using "runmlwin" command

This syntax utilises the user-written command 'runmlwin' which must be installed prior to use. The most recent version of MLwiN must be installed to be able to use this command and this package is available for use within Stata and R. Below we demonstrate the basic steps involved in implementing linear spline multilevel modelling suing "runmlwin" in Stata. Code below assumes data are in long format and that a variable called "occasion" exists identifying the ordering of observations within individuals. Sample code below applies to length/height from birth to five years.

Generate the spline variable

First, three new variables are created: s1 (spline 1 from birth to 6 months), s2 (6 months to 2 year), s3 (2 years to 5 years).

```
mkspline s1_birth_6m 27 s2_6m_2 107 s3_2_max = age_lw
```

Generate a constant term

MLwiN does not automatically include a constant term, so this must be generated and included in models.

```
gen cons=1
```

Identify the location of MLwiN

```
global MLwiN_path "C:\Program Files\MLwiN v3.05\mlwin.exe"
```

Run the multilevel model, sorting the data by person and occasion/age first.

```
sort study_id age
runmlwin length cons s1_birth_6m s2_6m_2 s3_2_max ///
level2 (study_id: cons  s1_birth_6m s2_6m_2 s3_2_max ,  reset(var) residuals (res, var)) ///
level1 (occ: age_lw, reset(var) diag) nopause maxiterations(150)
```

Adding covariates

The following assumes covariates are binary and coded 0 and 1 or for covariates with multiple categories, dummy variables have been created. The addition of continuous covariates should be undertaken in the same manner as for categorical covariates but continuous covariates should be centred on the mean so that the baseline trajectory in the model is for the individuals with the mean level of the continuous covariate. Here we demonstrate the steps required for addition of sex as a covariate.

Multiply covariate by splines

Once the covariate is coded in the format of 0/1 representing 0 for the baseline category, we multiply the covariate by the splines, creating interaction terms for inclusion in our model.

```
gen s1_birth_6m_fem = s1_birth_6m*female
gen s2_6m_2_fem = s2_6m_2*female
gen s3_2_max_fem = s3_2_max*female
```

Run model now including covariate terms

The model is then ran as before but this time including a term for the covariate in question, here “female” and each of the above female*spline interaction terms generated. This allows the mean trajectory to differ for females and males. Because in this example the variable female is coded 0 for male and 1 for female the baseline trajectory is now for males with coefficients for “female”, s1_birth_6m_fem, s2_6m_2_fem, s3_2_max_fem representing the difference in the intercept, spline 1 and spline 2 and spline 3 in females compared with males.

```
sort study_id age
runmlwin length cons s1_birth_6m s2_6m_2 s3_2_max female2*, ///
level2 (study_id: cons  s1_birth_6m s2_6m_2 s3_2_max ,  reset(var) residuals (res, var)) ///
level1 (occ: age_lw, reset(var) diag) nopause maxiterations(150)
```