

PEDIATRIC ORIGINAL ARTICLE

Growth trajectories in early childhood, their relationship with antenatal and postnatal factors, and development of obesity by age 9 years: results from an Australian birth cohort study

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BACKGROUND: In an era where around one in four children in the United Kingdom, the United States, and Australia are overweight or obese, the development of obesity in early life needs to be better understood. We aimed to identify groups of children with distinct trajectories of growth in infancy and early childhood, to examine any association between these trajectories and body size at age 9, and to assess the relative influence of antenatal and postnatal exposures on growth trajectories.

DESIGN: Prospective Australian birth cohort study.

SUBJECTS AND METHODS: In total, 557 children with serial height and weight measurements from birth to 9 years were included in the study. Latent class growth models were used to derive distinct groups of growth trajectories from birth to age 3½ years. Multivariable logistic regression models were used to explore antenatal and postnatal predictors of growth trajectory groups, and multivariable linear and logistic regression models were used to examine the relationships between growth trajectory groups and body size at age 9 years.

RESULTS: We identified four discrete growth trajectories from birth to age 3½ years, characterised as low, intermediate, high, or accelerating growth. Relative to the intermediate growth group, the low group had reduced z-body mass index (BMI) (−0.75 s.d.; 95% confidence interval (CI) −1.02, −0.47), and the high and accelerating groups were associated with increased body size at age 9 years (high: z-BMI 0.70 s.d.; 95% CI 0.49, 0.62; accelerating: z-BMI 1.64 s.d.; 95% CI 1.16, 2.11). Of the antenatal and postnatal exposures considered, the most important differentiating factor was maternal obesity in early pregnancy, associated with a near quadrupling of risk of membership of the accelerating growth trajectory group compared with the intermediate growth group (odds ratio (OR) 3.72; 95% CI 1.15, 12.05).

CONCLUSIONS: Efforts to prevent childhood obesity may need to be embedded within population-wide strategies that also pay attention to healthy weight for women in their reproductive years.

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INTRODUCTION

In an era where around one in four children in the United Kingdom, the United States, and Australia are classified as overweight or obese, there is a need to understand the development of obesity in early life. Weight at birth and accelerated postnatal growth are recognised predictors. These factors—and their determinants—are likely to be linked, but there are few integrated investigations, partly due to the relatively simple statistical approaches commonly employed.

To elaborate, a large systematic review of 66 studies (that included a meta-regression) recently demonstrated that birth weight is positively correlated to subsequent risk of overweight over almost the entire spectrum of birth weight.¹ Only at very low birth weights was there an indication of a J-shape, based on three studies of infants with birth weights < 1500 g. (The nadir of the curve occurred around 2000 g, and the risk of overweight in children with birth weights of < 1500 g was only slightly elevated, comparable to that of children weighing 2500 g.) Other systematic reviews consistently implicate early rapid weight gain in the development of obesity (for example, Weng *et al.*,² Brisbois *et al.*³

and Monasta *et al.*⁴). Accelerated postnatal growth is known to occur in infants who were born small for gestational age, but these are a fraction of all births. There may be other groups of infants that undergo rapid postnatal growth, but this has received little attention.⁵

Characterizing trajectories of body mass index (BMI) from birth provides a way to connect birth weight and subsequent growth paths.⁶ It also allows investigation of common determinants that may include maternal characteristics, behaviours and pregnancy complications.^{5,7} Recent studies that consider growth across childhood and adolescence suggest a small number of distinct growth trajectories, with three^{8–10} or four^{11–13} trajectories commonly reported, broadly corresponding to groups of children characterised as never overweight, chronically overweight, accelerating, or declining. Haga *et al.*¹⁴ derived trajectories from 11 repeated measurements of BMI between birth and age 12 years, and reported a five-group model for boys, and a six-group model for girls. No study has specifically focussed on growth trajectories in the early years of life, mainly due to limited data points in this period. Findings on underlying

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determinants are conflicting, with control for confounding generally poor.⁵

Therefore, the aims of the present paper were threefold. First, we aimed to examine growth in early childhood and identify groups of children with distinct trajectories of growth. Second, we aimed to examine any association between different trajectories of growth in early life and body size at age 9 years. Finally, we aimed to assess the relative influence of different antenatal and postnatal exposures on identified trajectories of growth.

MATERIALS AND METHODS

Sample and study design

The Generation 1 study is a prospective cohort study of women and their children established in Adelaide, South Australia between 1998 and 2000. Briefly, women were recruited ≤ 16 weeks of pregnancy at a public hospital or through the rooms of three obstetricians in private practice. Eligible women were aged ≥ 18 years, Caucasian, and free from certain conditions known to affect fetal growth.¹⁵ The University of Adelaide Human Research Ethics Committee reviewed and approved the study and all study procedures were conducted in accordance with the Helsinki declaration.

A total of 557 women completed the pregnancy phase of the study and had a live singleton baby. The sample of mothers was broadly representative of all women who gave birth in South Australia during the cohort's establishment.¹⁵

Mothers and children were followed up during the child's infancy and childhood. Data were collected at 16 and 32 weeks gestation, birth, at ages 3, 6, 9 and 12 months, and at 2, 3½, 5 and 9 years. Data pertaining to both the children and their wider family circumstances were collected *via* personal interviews on all but two occasions (data collected by phone at 3 months and post at 5 years).

Measures of child body size

Measurements of body size were taken at birth, 6, 9 and 12 months, and 2, 3½ and 9 years using protocols based on World Health Organization¹⁶ guidelines. Special arrangements were made for midwives to weigh and measure the study children at birth. Standardised measures of weight at 6, 9 and 12 months, and 2 and 3½ years (Heine S-83161 scales at < 3 years, Tanita TBF 531 scales, Tokyo, Japan, at 3½ years) and height/length (using a board and tape measure) were made. At 9 years, weight (using Tanita TBF 521 body fat scales, Tokyo, Japan) and height (using portable stadiometers, Invicta, Model no. 0955, Invicta Plastics Limited, Leicester, UK) were measured.

BMI at each time point was derived as $\text{weight}/\text{height}^2$ (kg m^{-2}). Age and sex-adjusted standardised weight, height and BMI (hereafter *z*-weight, *z*-height and *z*-BMI, respectively) were derived using the 1990 standards for British children.¹⁷ Gestational age was incorporated in the calculation of the birth *z*-scores only. BMI at age 9 years was also categorised using the IOTF (International Obesity Task Force) cutoffs based on the child's age and sex, to match the adult BMI cutoffs for overweight/obesity.¹⁸ The categories of overweight and obese were combined, as were the normal and underweight categories, resulting in a binary variable (normal/underweight vs overweight/obese).

Antenatal and postnatal exposures

Maternal height and weight were measured at the early pregnancy interview, and BMI was calculated subsequently. Based on a review of factors associated with accelerated growth,⁵ we hypothesised that self-reported maternal smoking in late pregnancy, parity, measured maternal weight change between early and late pregnancy accounting for weeks elapsed, gestational age at term and child sex were important antenatal exposures that may predict different growth trajectories across early childhood. We also hypothesised that gestational diabetes (based on antenatal records and maternal report) and pregnancy induced hypertension (from antenatal records) could be important predictors of discrete growth trajectories.¹ The two postnatal exposures we considered were duration of exclusive breastfeeding⁵ and timing of introduction of solid food.⁹ We considered two alternative categorizations of breastfeeding (breast milk exclusively at 6 weeks, breast and formula at 6 weeks, formula exclusively at 6 weeks); (breast milk exclusively at 12 weeks, breast and formula at 12 weeks, formula exclusively at 12 weeks). The timing of introduction of solids was classified as < 12 weeks, 12 to < 16 weeks, 16

to < 20 weeks and ≥ 20 weeks. We also considered maternal age at birth and maternal educational attainment by late pregnancy as potentially important background variables that captured socioeconomic aspects of the mothers' lives at the time of their child's birth.

Statistical analysis

We used latent class growth models (LCGMs) to identify distinct patterns of growth across infancy and early childhood up to age 3½ years.¹⁹ Such models use a semi-parametric approach to identify a set of curves (the trajectories) that capture the main features of the data, with each curve representing a different trajectory group. Individuals within a given trajectory group show similar trajectories to each other, and are more alike than individuals who are classified as belonging to other, distinct trajectory groups. Unlike traditional growth curve modelling, where a single average population growth trajectory is assumed, LCGMs do not assume a sole underlying growth trajectory and allow for heterogeneity within the population under consideration.

The distribution of *z*-BMI across six time points in infancy and early childhood (birth, 6, 9, 12 months, 2 years, 3½ years) was analysed with LCGMs, with polynomial functions up to order 5 considered. Child age (in days) at each time point was standardised and used in the modelling.²⁰ The variation (that is, residuals) of *z*-BMI within each group was assumed to be normally distributed. Children with at least one *z*-BMI measurement were included in the analysis ($n=556$) for the LCGM component.

We considered LCGMs with up to 12 trajectory groups and identified the best-fitting model based on: (i) the model with the highest Bayesian Information Criterion value, with a minimum 3-point change in absolute Bayesian Information Criterion between models needed for acceptance of an improved model; (ii) the most parsimonious trajectory shape with statistically significant polynomial coefficients; (iii) whether additional trajectories revealed important features in the data; and (iv) interpretability.²¹

Multiple linear or logistic regression analyses, as appropriate, were used to investigate any relationship between the identified trajectories and a number of measures of body size at age 9 years. Children with anthropometric measurements at age 9 years were included in these analyses ($n=443$).

Multinomial logistic regression analyses were used to examine the effects of antenatal and postnatal exposures on the growth trajectories of the child. Each of the exposures was initially considered in a separate regression model. Maternal age and education were included in all fitted models. The exposures with $P \leq 0.2$ in this initial stage were then included in a multivariable regression model (along with age and education), so as to better understand the joint role of antenatal and postnatal factors in the differentiation of growth trajectories. All available data were used in these models ($n=556$).

Under an assumption of missing at random, we used multiple imputation to assess the impact of missing values on our results. Missing values were imputed using chained equations with all available data for the antenatal and postnatal exposures.²² One hundred imputed data sets were created and analyses were subsequently run for each imputed data set. Inferences for the regression coefficients from these analyses were obtained by combining the results from the imputed data sets using Rubin's rules.²³

All analyses were conducted using SAS version 9.3 (SAS Inc., Cary, NC, USA). PROC TRAJ²⁰ was used in the derivation of the LCGM trajectories, and PROC MI was used in the multiple imputation analyses.

RESULTS

Selected characteristics of the study children and their families are presented in Table 1. As shown, the mean maternal age at birth of the study child was 29.8 years (s.d. 5.0), and almost half of the mothers had not completed high school before the birth of their child. Half of the mothers had a BMI in excess of 25 kg m^{-2} in early pregnancy. At age 9 years, the average BMI of the study children was 17.9 kg m^{-2} (s.d. 3.2). A total of 23% of the children were classified as overweight or obese according to IOTF criteria at this age.

Table 1. Summary of maternal and child characteristics among 556 families^a in the Generation 1 cohort

Characteristic	Summary
Maternal age at birth mean (s.d.)	29.8 (5.0)
Maternal education <i>n</i> (%)	
HS not completed	188 (33.8)
HS not completed, TAFE or Univ. completed	86 (15.5)
HS completed only	97 (17.4)
HS completed, TAFE completed	86 (15.5)
HS completed, Univ. completed	99 (17.8)
Child sex male <i>n</i> (%)	274 (49.3)
Parity, ≥ 1 previous child <i>n</i> (%)	370 (66.5)
Maternal height (cm) mean (s.d.)	163.5 (6.2)
Maternal early pregnancy BMI (kg m ⁻²) mean (s.d.)	26.2 (5.6)
Maternal early pregnancy BMI category <i>n</i> (%)	
< 25 kg m ⁻²	278 (50.0)
25 to < 30 kg m ⁻²	159 (28.6)
≥ 30 kg m ⁻²	119 (21.4)
Maternal early pregnancy weight (kg) mean (s.d.)	70.1 (15.1)
Gestational age at early pregnancy measurement (weeks) mean (s.d.)	14.5 (2.0)
Maternal late pregnancy weight (kg) mean (s.d.) (<i>n</i> = 548)	78.6 (14.6)
Gestational age at late pregnancy measurement (weeks) mean (s.d.)	32.6 (1.7)
Maternal early to late pregnancy weight change (kg) mean (s.d.) (<i>n</i> = 548)	8.3 (3.9)
Gestational age difference from early to late pregnancy measurement (weeks) mean (s.d.)	18.1 (2.5)
Pregnancy induced hypertension <i>n</i> (%)	62 (11.2)
Gestational diabetes <i>n</i> (%) (<i>n</i> = 535)	31 (5.8)
Smoking during pregnancy <i>n</i> (%)	119 (21.4)
Gestational age at delivery (weeks) mean (s.d.)	39.4 (1.6)
Breastfeeding status at 6 weeks <i>n</i> (%) (<i>n</i> = 548)	
Sole breastfeeding at 6 weeks	298 (54.4)
Breastfeeding and formula at 6 weeks	34 (6.2)
Sole formula at 6 weeks	216 (39.4)
Breastfeeding status at 12 weeks <i>n</i> (%) (<i>n</i> = 548)	
Sole breastfeeding at 12 weeks	219 (40.0)
Breastfeeding and formula at 12 weeks	56 (10.2)
Sole formula at 12 weeks	273 (49.8)
Timing of introduction of child to solid food <i>n</i> (%) (<i>n</i> = 530)	
< 12 weeks	67 (12.6)
12 to < 16 weeks	116 (21.9)
16 to < 20 weeks	216 (40.8)
≥ 20 weeks	131 (24.7)
Child weight at birth (kg) mean (s.d.)	3.4 (0.5)
Child z-weight at birth mean (s.d.)	0.15 (1.0)
Child length at birth (cm) mean (s.d.)	50.2 (2.3)
Child z-length at birth mean (s.d.) (<i>n</i> = 551)	0.012 (1.0)
Child weight at 9 years (kg) mean (s.d.) ^b	34.4 (8.3)
Child z-weight at 9 years mean (s.d.) ^b	0.41 (1.1)
Child height at 9 years (cm) mean (s.d.) ^b	138.0 (6.5)
Child z-height at 9 years mean (s.d.) ^b	0.25 (1.0)
Child BMI at 9 years (kg m ⁻²) mean (s.d.) ^b	17.9 (3.2)
Child z-BMI at 9 years mean (s.d.) ^b	0.41 (1.2)
Child overweight at 9 years <i>n</i> (%) ^b	77 (17.4)
Child obese at 9 years <i>n</i> (%) ^b	26 (5.9)

Abbreviations: BMI, body mass index; HS, High School; TAFE, Technical and Further Education College; Univ., University. ^aUnless otherwise shown. ^b*n* = 443.

Growth trajectories

The best-fitting LCGM identified four distinct groups, which we labelled as 'low' (84 children, 15%), 'intermediate' (256 children, 46%), 'high' (194 children, 35%) and 'accelerating' (22 children, 4%). The trajectories were generally characterised by birth size and postnatal growth in the first 6 months of life, with relatively parallel mean growth trajectories across the subsequent period from 6 months to 3½ years of age (as shown in Figure 1). The low trajectory group was typically born with a z-BMI close to zero

(birth weight mean 3.2 kg, s.d. 0.4), followed by pronounced decelerated postnatal growth to 6 months of age, and then a standard growth pattern through to age 3½ years. The intermediate trajectory group was also born with a z-BMI close to zero (birth weight mean 3.4 kg, s.d. 0.5), showed a more modest deceleration in postnatal growth to age 6 months compared with the low group, then a pattern of growth in parallel to those in the low group from 6 months to age 3½ years. The BMI at birth for the high trajectory group was around one standard deviation above the standardised mean (birth weight mean 3.6 kg, s.d. 0.5). The final identified group showed an accelerating growth trajectory, with an initially high birth z-BMI (birth weight mean 3.8 kg, s.d. 0.7) and then a linear upward pattern of growth to age 2 years before an apparent plateau in z-BMI to age 3½ years.

Effect of growth trajectories on obesity at 9 years

Of the children classified into the intermediate growth trajectory group, 9.0% were overweight and 1.2% were obese at age 9 years. In the low growth trajectory group, these values were 2.4% and 1.2%, respectively, at age 9 years. In the high and accelerating groups, at age 9 years the analogous figures were 23.2% overweight and 8.2% obese (high growth trajectory) and 31.8% overweight and 27.3% obese (accelerating growth trajectory), respectively.

Adjusted results from the regression of body size at 9 years on growth trajectories are shown in Table 2. Overall, the low trajectory group had reduced body size, and the high and accelerating groups increased body size at 9 years compared with the intermediate growth group. There was also some evidence of a dose-response relationship. Compared with the intermediate growth trajectory, the low group had a predicted mean reduction of 0.75 in z-BMI at age 9 years (95% confidence interval (CI) -1.02, -0.47). The high group had an increase of 0.70 (95% CI 0.49, 0.92) and the accelerating group a larger predicted increase of 1.64 (95% CI 1.16, 2.11). A similar pattern of results was observed for the relationship of z-weight and z-height with the different trajectory groups.

Those children in high and accelerating growth trajectory groups in childhood also had greatly increased odds of overweight/obesity at age 9 years compared with the children in the intermediate growth trajectory group (odds ratio (OR) high: 4.3; 95% CI 2.5, 7.3; OR accelerating 15.4; 95% CI 5.2, 45.1).

Effect of antenatal and postnatal exposures on growth trajectories

The estimated effects of the antenatal and postnatal exposures, adjusted for maternal age and education, on the odds of membership of the discrete growth trajectory groups are presented in Table 3. Three of the antenatal factors—higher maternal BMI in early pregnancy, male sex and multiparity—were significantly associated with increased odds of being in the accelerating trajectory relative to the intermediate trajectory.

Of note, maternal smoking in pregnancy, gestational age, gestational weight gain, gestational diabetes and pregnancy-induced hypertension were not statistically significant antenatal factors in the models we fitted. Neither duration of exclusive breastfeeding nor the timing of introduction to solids was significantly associated with the growth trajectories.

Further examination of the effect of maternal BMI suggested that an early pregnancy weight difference of 10 kg was associated with greater odds of membership of the high (OR 1.16; 95% CI 1.01, 1.34) and accelerating trajectory groups (OR 1.54; 95% CI 1.16, 2.05). There was some suggestion of an effect of inverse height², such that children of shorter women were more likely to be in the high trajectory group. The magnitude of effect differed according to the relative heights of the women being compared, and was larger for shorter women.

Results from the multiple imputation analyses for relevant exposures (also presented in Table 3) were very similar to those from the complete case analyses.

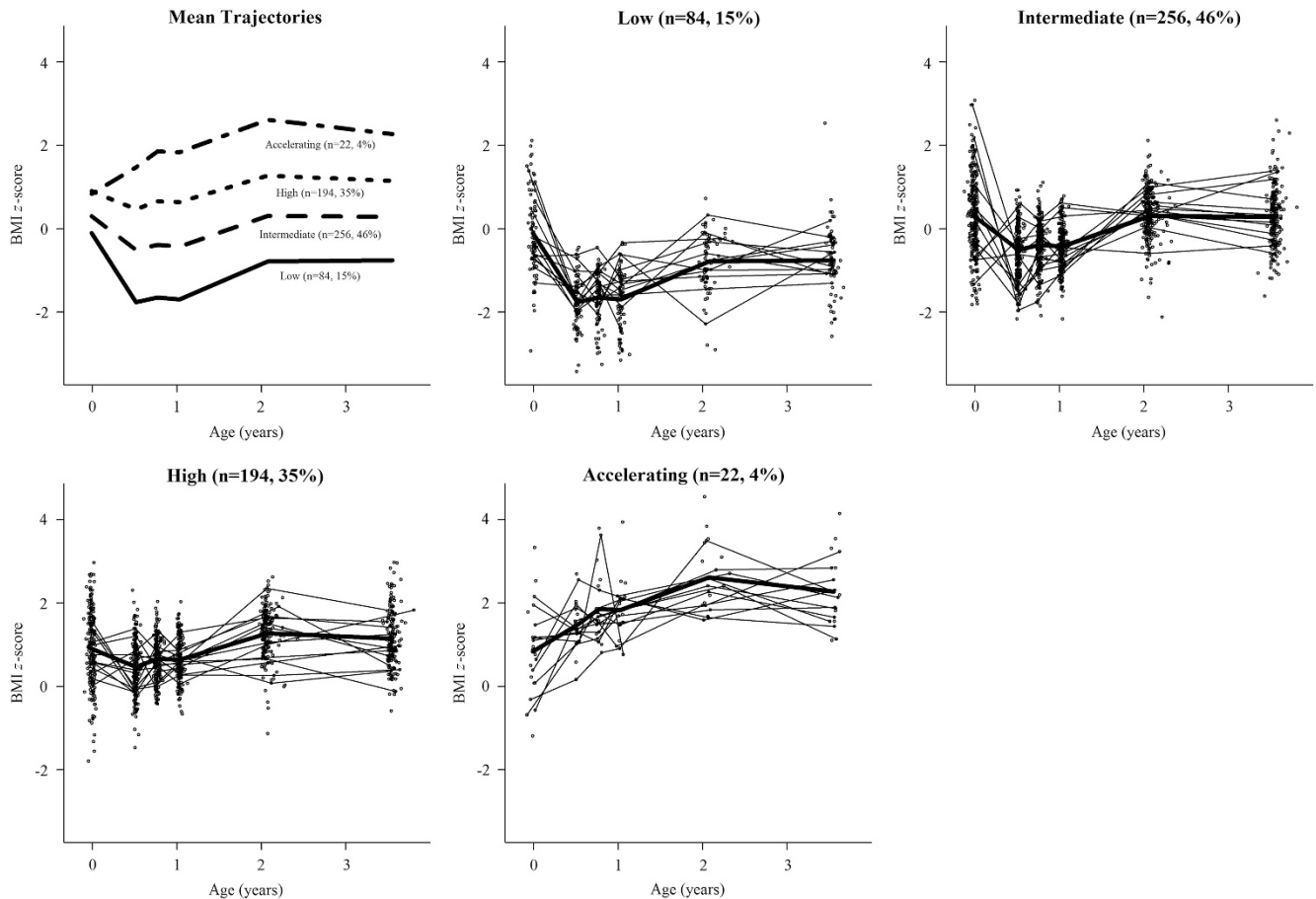


Figure 1. Summary of four z-BMI growth trajectory groups. Trajectories for 10 randomly selected children within each group are shown (joined line segments). Solid line in each plot indicates mean trajectory within that group.

Table 2. Effect of growth trajectory group on z-BMI, BMI category, z-weight and z-height at age 9 years, adjusted for maternal age and educational attainment in late pregnancy ($n = 443$)^a

Growth trajectory group	z-BMI ^b Mean (95% CI)	BMI category ^c Odds ratio (95% CI)	z-weight ^d Mean (95% CI)	z-height ^e Mean (95% CI)
Low	-0.49 (-1.16, 0.18)	0.29 (0.09, 1.00)	-0.68 (-1.34, -0.02)	-0.62 (-1.30, 0.05)
Intermediate	0.26 (-0.38, 0.90)	Reference	0.04 (-0.58, 0.67)	-0.26 (-0.90, 0.39)
High	0.97 (0.32, 1.61)	4.26 (2.50, 7.26)	0.54 (-0.09, 1.17)	-0.23 (-0.87, 0.42)
Accelerating	1.90 (1.13, 2.67)	15.36 (5.24, 45.05)	1.46 (0.71, 2.21)	0.38 (-0.40, 1.15)

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio. ^aAge- and sex-specific BMI, weight and height z-scores based on a 1990 UK reference population;¹⁷ BMI category = overweight/obese vs normal/underweight based on International Obesity Task Force cutoffs (Cole *et al.*¹⁷). ^b $R^2 = 0.275$. ^c $R^2 = 0.168$; Max-rescaled $R^2 = 0.254$. ^d $R^2 = 0.226$. ^e $R^2 = 0.057$.

Table 4 presents results from the final multivariable logistic regression model. In Model A, we initially included the three antenatal factors identified along with the week at which maternal BMI was measured in early pregnancy. As shown, maternal BMI and parity were retained. The effect of parity had a very wide corresponding 95% CI, reflecting that there was only one child with no older siblings in the accelerating growth trajectory group. For children of mothers who were obese in early pregnancy, the odds of being in the accelerating growth trajectory were 3.7 times those of children of mothers with BMI < 25 in early pregnancy, compared with the intermediate growth trajectory. There was some suggestion of a dose-response effect for obese mothers, with their offspring having reduced odds of membership of the low trajectory group, and slightly increased odds of membership of the high trajectory group.

In the alternative Models B and C, we considered the effects of maternal height and weight separately. Model B showed each additional 10 kg of maternal weight in early pregnancy was associated with increased odds of high (OR 1.14; 95% CI 1.00, 1.30) and accelerating (OR 1.41, 95% CI 1.08, 1.84) growth trajectory group membership. There was some evidence of an effect of maternal height on child growth trajectory group membership, similar to the results presented in Table 3. In Model C, where we examined the role of weight in early pregnancy independent of maternal stature, we observed a similar pattern of effect of pregnancy weight to that when maternal height was included in the statistical models. Notably, there was no evidence of a significant effect of gestational weight gain (either in interaction with BMI or as a main effect) in our fitted models.

Table 3. Effect of antenatal and postnatal exposures on child's z-BMI^a trajectory group from complete case analysis (*n* = 556 unless otherwise shown)

	Low trajectory OR (95% CI)	High trajectory OR (95% CI)	Accelerating trajectory OR (95% CI)	P-value ^b
<i>Antenatal exposures</i>				
Child sex male	0.64 (0.39, 1.05)	0.73 (0.50, 1.06)	2.40 (0.91, 6.36)	0.028
Gestational age at delivery	1.09 (0.92, 1.28)	1.07 (0.95, 1.21)	1.15 (0.84, 1.57)	0.557
Parity ≥ 1 previous children	0.65 (0.38, 1.12)	1.24 (0.81, 1.90)	14.60 (1.86, 114.43)	0.010
Maternal smoking in pregnancy	0.81 (0.43, 1.51)	0.73 (0.45, 1.20)	1.43 (0.53, 3.84)	0.456
<i>BMI in early pregnancy^c</i>				
< 25 kg m ⁻² (referent)	1.00	1.00	1.00	0.004
25 to < 30 kg m ⁻²	0.51 (0.27, 0.96)	1.35 (0.87, 2.10)	2.76 (0.87, 8.82)	
≥ 30 kg m ⁻²	0.51 (0.25, 1.03)	1.42 (0.86, 2.32)	4.40 (1.38, 14.03)	
Weight in early pregnancy difference of +10 kg	0.77 (0.62, 0.96)	1.16 (1.01, 1.34)	1.54 (1.16, 2.05)	< 0.001
Weight gain early pregnancy to late pregnancy (<i>n</i> = 548)	0.98 (0.91, 1.05)	1.01 (0.96, 1.07)	1.01 (0.90, 1.13)	0.812
Inverse maternal height squared: difference of -0.05 m from 1.70 m	1.01 (0.82, 1.24)	1.21 (1.04, 1.41)	1.23 (0.87, 1.74)	0.069
difference of -0.05 m from 1.80 m	1.01 (0.85, 1.20)	1.17 (1.03, 1.33)	1.19 (0.89, 1.60)	
Gestational diabetes (<i>n</i> = 535)	0.46 (0.13, 1.64)	0.48 (0.20, 1.19)	2.17 (0.57, 8.28)	0.126
Pregnancy induced hypertension	0.75 (0.33, 1.73)	0.93 (0.51, 1.70)	1.16 (0.32, 4.24)	0.903
<i>Postnatal exposures</i>				
<i>Timing of introduction to solids (<i>n</i> = 530)</i>				
16 to < 20 weeks (referent)	1.00	1.00	1.00	0.480
< 12 weeks	1.02 (0.42, 2.46)	1.58 (0.84, 2.97)	1.39 (0.25, 7.88)	
12 to < 16 weeks	1.11 (0.56, 2.23)	1.06 (0.62, 1.82)	3.47 (1.06, 11.32)	
≥ 20 weeks	1.34 (0.72, 2.52)	1.06 (0.64, 1.74)	1.77 (0.49, 6.42)	
<i>Breastfeeding at 6 weeks (<i>n</i> = 548)</i>				
Solely breastfed at 6 weeks (referent)	1.00	1.00	1.00	0.438
Formula and breast milk at 6 weeks	0.64 (0.17, 2.34)	1.55 (0.72, 3.37)	1.01 (0.12, 8.71)	
Solely formula at 6 weeks	0.83 (0.48, 1.43)	0.79 (0.52, 1.21)	1.52 (0.59, 3.92)	
<i>Breastfeeding at 12 weeks (<i>n</i> = 530)</i>				
Solely breastfed at 12 weeks (<i>n</i> = 530) (referent)	1.00	1.00	1.00	0.539
Formula and breast milk at 12 weeks	0.51 (0.18, 1.44)	1.21 (0.63, 2.30)	1.79 (0.41, 7.81)	
Solely formula at 12 weeks	0.67 (0.39, 1.16)	0.89 (0.58, 1.37)	1.35 (0.48, 3.83)	
<i>Multiple imputation results</i>				
<i>Antenatal exposures</i>				
Weight gain early pregnancy to late pregnancy	0.98 (0.91, 1.05)	1.01 (0.96, 1.07)	1.01 (0.90, 1.13)	0.827
Gestational diabetes	0.45 (0.13, 1.58)	0.50 (0.20, 1.24)	2.15 (0.56, 8.21)	0.138
<i>Postnatal exposures</i>				
<i>Timing of introduction to solids</i>				
16 to < 20 weeks (referent)	1.00	1.00	1.00	0.579
< 12 weeks	1.01 (0.42, 2.43)	1.52 (0.81, 2.84)	1.31 (0.23, 7.41)	
12 to < 16 weeks	1.12 (0.56, 2.24)	1.06 (0.62, 1.81)	3.21 (0.99, 10.40)	
≥ 20 weeks	1.32 (0.71, 2.46)	1.04 (0.63, 1.70)	1.70 (0.47, 6.15)	
<i>Breastfeeding at 6 weeks</i>				
Solely breastfed at 6 weeks (referent)	1.00	1.00	1.00	0.450
Formula and breast milk at 6 weeks	0.64 (0.17, 2.36)	1.55 (0.71, 3.37)	1.01 (0.12, 8.69)	
Solely formula at 6 weeks	0.83 (0.48, 1.42)	0.79 (0.52, 1.21)	1.53 (0.59, 3.93)	
<i>Breastfeeding at 12 weeks</i>				
Solely breastfed at 12 weeks (referent)	1.00	1.00	1.00	0.560
Formula and breast milk at 12 weeks	0.51 (0.18, 1.43)	1.17 (0.62, 2.24)	1.71 (0.39, 7.47)	
Solely formula at 12 weeks	0.67 (0.39, 1.15)	0.89 (0.58, 1.36)	1.33 (0.47, 3.76)	

Abbreviation: BMI, body mass index. Odds ratios (ORs) and 95% confidence intervals (95% CIs) are shown. Referent group for outcome is intermediate growth trajectory. All models adjusted for effect of maternal age and educational attainment in late pregnancy. ^aAge- and sex-specific standard deviation scores based on a 1990 UK reference population.¹⁷ ^bP-values for variables reflect an overall Wald χ^2 test for the inclusion of the set of variables. ^cAdjusted for week of measurement.

DISCUSSION

Our findings suggest that there are four discrete BMI trajectories from birth to age 3½ years, with features that can be characterised as low, intermediate, high or accelerating growth. The distinct growth trajectories were evident as early as 6 months of age. A graded effect of the four different trajectory groups on risk of

overweight/obesity at age 9 years was apparent, such that the low trajectory group was associated with reduced height and weight, and the high and accelerating groups were associated with increased body size in comparison with the intermediate growth group. Of the antenatal and postnatal exposures that we considered, the most important factor that differentiated between the

Table 4. Final models showing effect of antenatal and postnatal exposures on child's z-BMI trajectory group from complete case analysis ($n = 556$)

	Low trajectory	High trajectory	Accelerating trajectory	P-value
<i>Model A</i>				
Child sex male	0.62 (0.37, 1.03)	0.73 (0.50, 1.07)	2.32 (0.85, 6.32)	0.033
Parity ≥ 1 previous child	0.72 (0.41, 1.25)	1.21 (0.78, 1.87)	11.75 (1.48, 92.99)	0.037
BMI in early pregnancy				
< 25 kg m ⁻² (referent)	1.00	1.00	1.00	0.013
25 to < 30 kg m ⁻²	0.52 (0.28, 0.99)	1.32 (0.85, 2.06)	2.20 (0.67, 7.19)	
≥ 30 kg m ⁻²	0.51 (0.25, 1.05)	1.35 (0.82, 2.23)	3.72 (1.15, 12.05)	
<i>Model B</i>				
Child sex male	0.62 (0.37, 1.03)	0.74 (0.51, 1.08)	2.31 (0.85, 6.26)	0.035
Parity ≥ 1 previous child	0.70 (0.41, 1.22)	1.23 (0.79, 1.90)	12.78 (1.61, 101.43)	0.026
Weight in early pregnancy difference of +10 kg	0.77 (0.63, 0.95)	1.14 (1.00, 1.30)	1.41 (1.08, 1.84)	< 0.001
Inverse maternal height squared difference of -0.05 m from 1.70 m	0.98 (0.80, 1.20)	1.18 (1.02, 1.37)	1.21 (0.87, 1.70)	0.099
difference of -0.05 m from 1.80 m	0.98 (0.83, 1.16)	1.15 (1.02, 1.30)	1.18 (0.89, 1.56)	
<i>Model C</i>				
Child sex male	0.62 (0.37, 1.03)	0.73 (0.50, 1.07)	2.28 (0.84, 6.17)	0.034
Parity ≥ 1 previous children	0.70 (0.40, 1.21)	1.22 (0.79, 1.88)	12.21 (1.55, 96.46)	0.028
Weight in early pregnancy difference of +10 kg	0.78 (0.64, 0.95)	1.10 (0.97, 1.25)	1.36 (1.05, 1.77)	0.001

Abbreviation: BMI, body mass index. Odds ratios (95% confidence intervals) are shown. Referent group for outcome is intermediate growth trajectory. Models adjusted for effect of maternal age and educational attainment in late pregnancy are shown.

trajectories was maternal BMI in early pregnancy. In particular, maternal obesity in early pregnancy was associated with a fourfold risk of membership of the accelerating trajectory group for the offspring.

The growth trajectories that we identified were established, in the main, by 6 months of age. From this age through to 3½, the trajectories were relatively parallel, with little difference in the shape of z-BMI paths across the four different groups across this age span. In keeping with our results, Haga *et al.*¹⁴ showed broadly parallel z-BMI patterns from early childhood (around age 2 years in their study), with the exception of a group of girls they termed 'progressive average' with a z-BMI below average until age 5 years that then increased sharply to +1 s.d. by age 8 years, possibly associated with an early adiposity rebound. Our finding of four groups agrees with the results reported by Carter *et al.*,¹¹ based on five z-BMI measurements between ages 4 and 10, and those of Mustillo *et al.*,¹³ drawn from annual weight and height measurements between ages 9 and 16 years. While other authors have reported three distinct trajectory groups,^{8–10} these studies were limited by maternal reported heights and weights¹⁰ or did not analyse standardised BMI.^{8–9}

Our results also demonstrate that the broad groupings of growth that we identified had clearly detectable effects on body size at age 9 years, with the group of children in the high growth group in early childhood showing a fourfold increase in odds of overweight or obesity at age 9 years. Those children in the accelerated growth trajectory group in early childhood had a 15-fold increase in odds of overweight or obesity at age 9 years. While other studies have identified distinct trajectories of growth in early childhood (for example, Pryor *et al.*¹⁰), our work is novel in showing the growth groupings in early childhood appear to track to at least age 9.

The establishment of trajectories in infancy might suggest that feeding practices are important determinants of the course of growth in childhood. However, we did not find the duration of breastfeeding nor the timing of introduction of solids to have a role in distinguishing between growth trajectory groups. While meta-analyses suggest that infant breastfeeding is associated with a lower risk of overweight and obesity in later childhood, this evidence is largely derived from observational studies, with

residual confounding (especially from maternal factors including maternal obesity, smoking and socioeconomic status) and publication bias suggested to at least partially explain the relationship.²⁴ A recent large randomised trial did not show any beneficial effects of prolonged and exclusive breastfeeding on child height, weight or adiposity at age 6.5 years.²⁵

It is possible that the differentiation of growth trajectories in the first 6 months of life stem from conditions in pregnancy, but we did not find effects of gestational diabetes nor pregnancy induced hypertension (both managed according to current clinical guidelines). Instead, our analyses showed maternal BMI in early pregnancy was by far the most important determinant of the different growth trajectories. Our results also pointed to a relationship between parity and accelerated growth in early life, consistent with the positive association between greater size in early life and multiparity reported across three cohorts by Pizzi *et al.*²⁶ We note, however, the wide CI associated with our effect estimate for parous women, which precludes us from commenting further on the magnitude of the effect of parity. The systematic review by Chrestani *et al.*,⁵ of factors associated with rapid weight gain in early childhood, identifies primiparity, maternal smoking, lower birth weight and early weaning as potential determinants, but highlights many problems with the literature.

The influence of maternal BMI in early pregnancy on offspring's growth patterns is likely to reflect a complex interplay between genes, programming and the environment. Evidence of a direct effect of genes and their joint action on body composition, such as between fat and obesity associated and other (for example, IRX3) genes, is beginning to emerge.²⁷ The potential modification of gene expression by periconceptional maternal diet and pre-existing obesity may also be relevant. Animal experiments have shown that obese mice have more apoptotic ovarian follicles, smaller and fewer mature oocytes, and perturbed insulin-like growth factor signalling in the embryo. The live offspring display a growth restricted phenotype followed by high body weight post-weaning accompanied by glucose intolerance and increased body fat.²⁸ Maternal periconceptional obesity is also associated with increased oxidative stress during fetal development,²⁹ which contributes to the emergence of features of the metabolic syndrome, including fat mass in offspring.³⁰

The findings from this study must be interpreted with several caveats borne in mind. One limitation concerns the determination of the number of different trajectory groups, which was decided within the framework of LCGMs. Some children may be classified as belonging to a particular trajectory group but follow patterns of growth that are not typical of the majority of trajectories within that group. This can reflect variability in patterns within each group,³¹ a common issue with classification of trajectories using group-based modelling methods. While growth mixture modelling approaches remove the constraint on within-class variation in the LCGM method, disadvantages with such approaches have been highlighted with respect to interpretability and the identification of non-existent subclasses.³²

Another limitation in our study is that we were unable to take some potentially relevant covariates into account. Notably, we did not have a measure of paternal BMI during the gestational period. Measurements of infant weight and length were not made in the interval between birth and 6 months, so that a more nuanced analysis of the pace of growth in this period with respect to early life growth trajectories and their effects on body size at age 9 years was not possible. In addition, we do not have detailed measurements of size beyond age 3½ years, so were not able to consider adiposity rebound, although features of BMI trajectory have been shown to be related to the timing of adiposity rebound.³³ Another limitation that must be recognised is the possibility that the particular associations we observed are due to unmeasured variables; we cannot infer causality from the relationships we have established in this research.

Strengths of our study include the rigorous repeated measurement of body size during infancy and toddlerhood, the use of standardised BMIs rather than binary measures, information concerning a wide range of relevant predictors, and the heterogeneous sample that included mothers and children from a broad range of social circumstances.¹⁵

The wider literature on infant growth has expanded greatly over the last decade. A number of systematic reviews summarised the relationship between rapid infant growth (defined variously) and later risk of overweight or obesity, beginning with Monteiro and Victora³⁴ and Baird *et al.*³⁵ The third in this series³⁶ standardised rapid growth as a change in weight s.d. score of at least 0.67, which corresponded to a difference between the key centile bands displayed on growth charts (that is, 2nd, 10th, 25th, 50th, 75th, 90th and 98th centiles). While this definition of rapid growth may be most amenable to use in clinical settings, it remains an arbitrary cutoff that may not differentiate biologically risky growth from rapid growth that is not strongly associated with poor outcomes in terms of obesity or other health conditions. This is where LCGM is useful to distinguish groups of children that are biologically distinct in terms of their growth trajectories.

Numerous studies have, nevertheless, continued to define rapid growth as a change in weight s.d. score of at least 0.67 (or a close variant) to further define relationships with adverse outcomes, to consider determinants or, more recently, to develop screening tools or algorithms to determine which children should be targeted for intervention (for example, Weng *et al.*² and Monasta *et al.*⁴). The largest study with the latter aim was an individual-level meta-analysis of data from 10 cohort studies by Druet *et al.*³⁷ Each one-unit increase in weight s.d. between birth and 1 year doubled the risk of obesity in childhood but conferred only a 23% increase in risk of obesity in adulthood. Here the recent work of Odegaard *et al.*³⁸ is noteworthy: rapid growth in terms of weight (change in s.d. ≥ 0.67), considered for various periods between birth to age 2 years, was infrequently associated with overweight in early adulthood whereas rapid growth in terms of weight-for-length was strongly and consistently associated with overweight in early adulthood. Thus, there is evidence that length/height is an important consideration; it is likely that the predominance of

published research focussing on weight alone is partly a consequence of length/height measures being unavailable.

Accompanying the many investigations of the outcomes of rapid infant growth are questions about the aetiology or drivers. The most promising development in this area is arguably the superimposition by translation and rotation (SITAR) approach, with recent demonstration of different factors influencing infant size, growth velocity and tempo.²⁶ This complex modelling will advance aetiological understanding but does not immediately lend itself to accessible prediction algorithms or tools.

From a policy perspective, our results suggest that translation initiatives should target pre-pregnancy planning as a period to optimise maternal weight, with likely benefits for the future health of both mother and child. The importance of entering pregnancy with a normal range BMI to ensure the best trajectories of growth in offspring's early years should be incorporated in health promotion messages for women who are planning first pregnancies and for women who are already mothers. For the latter group, interactions with health professionals for scheduled child health visits may present opportunities for discussing the importance of entering subsequent pregnancies at a healthy weight.

In conclusion, we identified four BMI trajectories across birth to 3½ years of age. A clear gradient in the association between the four growth trajectory groups and risk of overweight/obesity at age 9 years was found. We also showed that maternal obesity in early pregnancy was associated with a near quadrupling of risk of offspring's membership of the accelerating growth trajectory group. These findings suggest that efforts to identify children at risk of obesity in later childhood must be embedded within population wide prevention strategies that also pay attention to healthy weight for women in their reproductive years.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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