

Supplementary methods

Foetal growth trajectories assessment

We used multilevel linear spline model¹⁻⁵ to assess foetal growth trajectories based on estimated foetal weight (EFW; in grams) of 14,482 ultrasound scans from 4,818 children. This model takes into account the within-individual correlation for repeatedly measured EFW and missing data under the assumption of ‘missing at random’. For the analysis, we included any child who had ≥ 1 fetal ultrasound scans. Birth weight was also included and treated as ‘EFW’ at another time-point (i.e. gestational age at birth).

Fractional polynomial model was first constructed to identify the best-fitting fetal growth trajectory for the whole sample. Based on the best-fitting curve, we first determined number of knots (i.e. two) and their potential locations (first knot at 26, 27 or 28 weeks; second knot at 36, 37 or 38 weeks) which could split the whole gestation into three periods. To finalise the location of the two knots, we ran multilevel linear spline models to calculate the Bayesian information criterion (BIC) for each combination of the potential locations of the two knots (a total of nine combinations). We chose 28 weeks (the cut-off of the third trimester) and 37 weeks (the cut-off of preterm birth) as the locations based on a combination of BIC values and interpretability of the location of knots. Based on these two knots, the entire gestation period was split into three: ‘mid-pregnancy’ (22-27 weeks), ‘early-third trimester’ (28-36 weeks) and ‘late-third trimester’ (37 weeks and above).

We then constructed the multilevel linear spline model, separately for boys and girls to obtain the EFW growth velocities during different periods. Gestational age when the ultrasound scan was performed was centred at 22 weeks. As previous studies,^{1, 3} the EFW was modelled as

$$EFW_{ij} = \beta_0 + \mu_{0i} + (\beta_1 + \mu_{1i})S_{1i} + (\beta_2 + \mu_{2i})S_{2i} + (\beta_3 + \mu_{3i})S_{3i} + e_{ij}$$

where

i represents the individual,

j represents gestational age,

β_0 , β_1 , β_2 and β_3 are the fixed coefficients, representing the population average intercept (EFW at 22 weeks) and average slopes (i.e. growth velocities) during ‘mid-pregnancy’ (22-27 weeks), ‘early-third trimester’ (28-36 weeks) and ‘late-third trimester’ (37 weeks and above), respectively,

μ_{0i} , μ_{1i} , μ_{2i} , and μ_{3i} are the random effects that represent deviations for individual i from the population average intercept and from the average slopes during ‘mid-pregnancy’, ‘early-third trimester’ and ‘late-third trimester’, respectively,

S_{1i} , S_{2i} and S_{3i} are the three linear splines defined by the two knots, representing the duration of weeks for individual i staying in each period.¹

The splines were constructed based on a piecewise linear function for gestational age; therefore, it is forced to be continuous at the knots. We used independent covariance structure for the random effects. We also tried an unstructured covariance matrix for the analysis initially, but this model failed to converge, probably due to the mistimed measurements at irregular intervals and the sample size not being large enough. The modelling was performed using *xtmixed* command in Stata. The actual splines are

shown in Figure S2. Residuals plots were generated to examine model fit for the multilevel linear model. The residuals appeared to be distributed symmetrically by the horizontal line ($y=0$) (Figure S3), suggesting that the model fit is appropriate.

Because a significant proportion (44%) of women had no ultrasound measurements at the first gestational interval (i.e. 22-27 weeks), we compared characteristics between these women and those who ultrasound scan at 22-27 weeks. There was no substantial difference between the two groups, although participants who had ultrasound data had a higher income and were more likely to be nulliparous (Table S11).

References

1. Norris T, Johnson W, Petherick E, Cameron N, Oddie S, Johnson S, et al. Investigating the relationship between fetal growth and academic attainment: secondary analysis of the Born in Bradford (BiB) cohort. *International journal of epidemiology*. 2018 Oct 1;47(5):1475-84.
2. Lampl M, Kusanovic JP, Erez O, Espinoza J, Gotsch F, Goncalves L, et al. Early rapid growth, early birth: accelerated fetal growth and spontaneous late preterm birth. *Am J Hum Biol*. 2009 Mar-Apr;21(2):141-50.
3. Howe LD, Tilling K, Matijasevich A, Petherick ES, Santos AC, Fairley L, et al. Linear spline multilevel models for summarising childhood growth trajectories: A guide to their application using examples from five birth cohorts. *Stat Methods Med Res*. 2016 Oct;25(5):1854-74.
4. Monjardino T, Amaro J, Fonseca MJ, Rodrigues T, Santos AC, Lucas R. Early childhood as a sensitive period for the effect of growth on childhood bone mass: Evidence from Generation XXI birth cohort. *Bone*. 2019 Oct;127:287-95.
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Table S1. Comparison of baseline characteristics of participants included in the analysis to those excluded due to unavailability of growth data at three years of age.

Variables	Included n=4,818	No growth data n=4,693
Maternal age (years), mean (SD)	29.2 (3.3)	28.9 (3.4)
Educational level (%)		
Middle school or below	7.2	12.1
Vocational or technical college	24.3	16.2
Undergraduate	56.0	50.5
Postgraduate	12.5	11.3
Monthly income (Yuan) (%)		
≤1500	9.5	10.8
1501-4500	29.7	33.3
4501-9000	44.4	39.7
≥9001	16.4	16.1
Pre-pregnancy BMI (kg/m ²), mean (SD)	20.4 (2.6)	20.3 (2.6)
Nulliparous (%)	88.2	86.7
Diabetes during pregnancy (%)	13.2	14.2
Hypertensive disorder in pregnancy (%)	2.7	2.2
Active/passive smoking during pregnancy (%)	29.6	31.2
Breastfeeding duration, months, mean (SD)	8.4 (3.7)	7.7 (1.9)

Tables S2. Number of ultrasound measurements for each gestational interval and for maternal pregnancy complications such as diabetes and hypertensive disorders

Characteristics	Number of ultrasound measurements	
	Median	Range
Diabetes during pregnancy		
No	3	1-7
Yes	3	1-7
Hypertensive disorders in pregnancy		
No	3	1-7
Yes	4	1-7
Gestational periods		
22-27 weeks	1	0-3
28-36 weeks	2	0-6
≥ 37 weeks	2	0-5

Table S3. Comparison of baseline characteristics of participants included in the validation sample (n=992) and the overall dataset (n=4818).

Variables	Validation sample n=992	Overall dataset n=4818
Maternal age (years), mean (SD)	29.2 (3.2)	29.2 (3.3)
Educational level (%)		
Middle school or below	6.2	7.2
Vocational or technical college	23.8	24.3
Undergraduate	56.6	56.0
Postgraduate	13.5	12.5
Monthly income (Yuan) (%)		
≤1500	9.3	9.5
1501-4500	28.0	29.7
4501-9000	46.4	44.4
≥9001	16.3	16.4
Pre-pregnancy BMI (kg/m ²), mean (SD)	20.5 (2.8)	20.4 (2.6)
Nulliparous (%)	88.8	88.2
Diabetes during pregnancy (%)	13.4	13.2
Hypertensive disorder in pregnancy (%)	2.1	2.7
Active/passive smoking during pregnancy (%)	29.8	29.6

Table S4. Comparison of characteristics of participants whose growth were measured from regular child health care clinics to participants whose growth were measured by cohort staff.

Variables	Cohort n=3,890	Other clinics n=928
Maternal age (years), mean (SD)	29.3 (3.3)	29.1 (3.3)
Educational level (%)		
Middle school or below	6.5	10.0
Vocational or technical college	23.9	26.1
Undergraduate	57.2	50.9
Postgraduate	12.4	13.0
Monthly income (Yuan) (%)		
≤1500	9.0	11.5
1501-4500	30.0	28.6
4501-9000	44.6	43.5
≥9001	16.4	16.4
Pre-pregnancy BMI (kg/m ²), mean (SD)	20.4 (2.6)	20.3 (2.7)
Nulliparous (%)	88.9	85.2
Diabetes during pregnancy (%)	13.2	13.2
Hypertensive disorder in pregnancy (%)	2.3	4.3
Active/passive smoking during pregnancy (%)	29.2	31.0
Breastfeeding duration, months, mean (SD)	8.5 (3.7)	8.0 (3.8)

Table S5. Missingness of variables

Variables	Missing data	
	n	%
<i>Maternal factors</i>		
Age	0	0
Educational level	0	0
Monthly income	118	2.5
Pre-pregnancy BMI	116	2.4
Parity	3	0.1
Diabetes during pregnancy	2	0.04
Hypertensive disorders in pregnancy	1	0.02
Active or passive smoking during pregnancy	25	0.5
Folic acid intake during pregnancy	27	0.6
<i>Child's factor</i>		
Z score of fetal size at 22 weeks	0	0
Z score of growth velocity at 22-27 weeks	0	0
Z score of growth velocity at 28-37 weeks	0	0
Z score of growth velocity at 37 weeks or above	0	0
Gestational age at birth	0	0
Sex	0	0
Breastfeeding duration by 12-month old	510	10.6
LAZ/HAZ at 3-years	157	3.3
WAZ at 3-years	118	2.4
BMIZ at 3-years	227	4.7
Outliers: LAZ/HAZ	47	1.0
Outliers: WAZ	24	0.5

BMI, body mass index; LAZ, length-for-age Z score; HAZ, height-for-age Z score; WAZ, weight-for-age z score; BMIZ, body mass index-for-age z score.

Table S6: Estimated fetal weight at 22 weeks and growth velocities for 22-27 weeks, 28-36 weeks and 37 weeks and above, based on multilevel linear spline models

Growth variables	Mean (95% CI)
<i>Females (n=2,285)</i>	
Fetal weight at 22 weeks (grams)	505.0 (500.3, 509.6)
Growth velocities at 22-27 weeks (grams/week)	84.4 (82.2, 86.5)
Growth velocities at 28-36 weeks (grams/week)	192.3 (190.5, 194.1)
Growth velocities at 37 weeks and above (grams/week)	164.1 (159.3, 168.7)
<i>Males (n=2,533)</i>	
Fetal weight at 22 weeks (grams)	525.5 (520.7, 530.2)
Growth velocities at 22-27 weeks (grams/week)	87.5 (85.3, 89.7)
Growth velocities at 28-36 weeks (grams/week)	196.7 (194.9, 198.5)
Growth velocities at 37 weeks and above (grams/week)	175.6 (170.8, 180.4)

Table S7. Comparison of effect sizes for one Z score increase in fetal growth between different gestational periods.

Comparison of effect sizes		P-value
Stunting		
22 nd week	versus 22-27 weeks	0.85
	versus 28-36 weeks	0.43
	versus ≥ 37 weeks	0.24
22-27 weeks	versus 28-36 weeks	0.42
	versus ≥ 37 weeks	0.23
28-36 weeks versus ≥ 37 weeks		0.93
Underweight		
22 nd week	versus 22-27 weeks	0.36
	versus 28-36 weeks	0.013
	versus ≥ 37 weeks	<0.0001
22-27 weeks	versus 28-36 weeks	0.018
	versus ≥ 37 weeks	<0.0001
28-36 weeks versus ≥ 37 weeks		0.28
At-risk overweight		
22 nd week	versus 22-27 weeks	0.20
	versus 28-36 weeks	0.90
	versus ≥ 37 weeks	0.015
22-27 weeks	versus 28-36 weeks	0.97
	versus ≥ 37 weeks	0.009
28-36 weeks versus ≥ 37 weeks		0.041
Overweight/obesity		
22 nd week	versus 22-27 weeks	0.42
	versus 28-36 weeks	0.35
	versus ≥ 37 weeks	0.022
22-27 weeks	versus 28-36 weeks	0.31
	versus ≥ 37 weeks	0.018
28-36 weeks versus ≥ 37 weeks		0.40

Table S8. Stratified analysis by pre-pregnancy BMI for associations between foetal growth Z scores and childhood growth outcomes

Periods	Stratum	Risk ratio (95% confidence interval)			
		Stunting	Underweight	At risk of overweight	Overweight/obesity
< 22 weeks	Underweight	0.61 (0.49, 0.78)	0.46 (0.38, 0.55)	1.33 (1.11, 1.58)	1.42 (0.93, 2.16)
	Normal	0.79 (0.63, 0.98)	0.53 (0.44, 0.63)	1.22 (1.12, 1.33)	1.32 (1.11, 1.57)
	Overweight/Obese	0.62 (0.41, 0.96)	0.34 (0.18, 0.64)	1.23 (1.00, 1.53)	1.74 (1.21, 2.51)
	P _{interaction}	0.141	0.036	0.368	0.066
22-27 weeks	Underweight	0.63 (0.50, 0.80)	0.47 (0.39, 0.57)	1.29 (1.09, 1.53)	1.43 (0.91, 2.27)
	Normal	0.78 (0.63, 0.97)	0.53 (0.45, 0.62)	1.24 (1.14, 1.36)	1.33 (1.11, 1.59)
	Overweight/Obese	0.60 (0.38, 0.93)	0.36 (0.18, 0.71)	1.23 (0.99, 1.52)	1.87 (1.32, 2.66)
	P _{interaction}	0.126	0.045	0.511	0.040
28-36 weeks	Underweight	0.78 (0.55, 1.10)	0.75 (0.54, 1.06)	1.67 (1.28, 2.20)	1.33 (0.74, 2.42)
	Normal	0.93 (0.67, 1.28)	0.71 (0.52, 0.98)	1.11 (0.97, 1.28)	1.14 (0.82, 1.59)
	Overweight/Obese	0.62 (0.33, 1.16)	0.42 (0.22, 0.79)	1.26 (0.98, 1.61)	1.42 (0.79, 2.56)
	P _{interaction}	0.041	0.084	0.064	0.024
≥37 weeks	Underweight	0.88 (0.66, 1.18)	0.79 (0.61, 1.02)	1.14 (0.94, 1.39)	0.78 (0.41, 1.47)
	Normal	0.77 (0.65, 0.91)	0.73 (0.62, 0.87)	1.06 (0.95, 1.17)	1.13 (0.88, 1.45)
	Overweight/Obese	0.78 (0.52, 1.16)	0.68 (0.32, 1.43)	1.12 (0.92, 1.38)	0.92 (0.64, 1.32)
	P _{interaction}	0.772	0.797	0.066	0.874

All models were adjusted for maternal age, education level, monthly income, parity, active or passive smoking during pregnancy, diabetes during pregnancy, hypertensive disorders in pregnancy, and breastfeeding duration. Models for 28-36 weeks (early-third trimester) were additionally adjusted for growth in 22-27 weeks (mid-pregnancy); models for ≥37 weeks (late-third trimester) were additionally adjusted for growths in 22-27 weeks (mid-pregnancy) and 28-36 weeks (early-third trimester).

Table S9. Stratified analysis by maternal diabetes for associations between foetal growth Z scores and childhood growth outcomes

Periods	Stratum	Risk ratio (95% confidence interval)			
		Stunting	Underweight	At risk of overweight	Overweight/obesity
< 22 weeks	Non-diabetes	0.71 (0.60, 0.84)	0.48 (0.43, 0.54)	1.31 (1.21, 1.41)	1.41 (1.19, 1.68)
	Diabetes	0.67 (0.44, 1.02)	0.47 (0.27, 0.81)	1.03 (0.83, 1.29)	1.45 (1.12, 1.89)
	P _{interaction}	0.917	0.789	0.068	0.802
22-27 weeks	Non-diabetes	0.71 (0.60, 0.83)	0.49 (0.44, 0.56)	1.31 (1.21, 1.42)	1.44 (1.21, 1.71)
	Diabetes	0.66 (0.42, 1.05)	0.44 (0.25, 0.77)	1.08 (0.87, 1.34)	1.47 (1.13, 1.92)
	P _{interaction}	0.903	0.977	0.124	0.810
28-36 weeks	Non-diabetes	0.84 (0.67, 1.07)	0.69 (0.55, 0.86)	1.32 (1.17, 1.49)	1.20 (0.88, 1.63)
	Diabetes	0.70 (0.33, 1.48)	0.81 (0.38, 1.71)	0.94 (0.68, 1.30)	1.50 (0.88, 2.56)
	P _{interaction}	0.641	0.954	0.016	0.409
≥37 weeks	Non-diabetes	0.80 (0.68, 0.93)	0.76 (0.66, 0.87)	1.07 (0.98, 1.17)	1.01 (0.80, 1.27)
	Diabetes	0.90 (0.63, 1.28)	0.81 (0.49, 1.35)	1.22 (0.97, 1.55)	1.30 (0.85, 1.99)
	P _{interaction}	0.930	0.933	0.978	0.125

All models were adjusted for maternal age, education level, monthly income, pre-pregnancy body mass index, parity, active or passive smoking during pregnancy, hypertensive disorders during pregnancy, and breastfeeding duration. Models for 28-36 weeks (early-third trimester) were additionally adjusted for growth in 22-27 weeks (mid-pregnancy); models for ≥37 weeks (late-third trimester) were additionally adjusted for growths in 22-27 weeks (mid-pregnancy) and 28-36 weeks (early-third trimester).

Table S10. Association between foetal growth Z scores and child growth outcomes after excluding women with hypertensive disorders in pregnancy

Fetal growth variables	Risk ratio (95% confidence interval)				Regression coefficients (95% confidence interval)		
	Stunting	Underweight	At risk of overweight	Overweight/ obesity	Length/height-for-age Z score	Weight-for-age Z score	BMI-for-age Z score
Size in early pregnancy	0.71 (0.61, 0.83)	0.48 (0.42, 0.55)	1.26 (1.17, 1.36)	1.46 (1.27, 1.68)	0.17 (0.14, 0.20)	0.26 (0.23, 0.29)	0.19 (0.16, 0.22)
Growth in mid-pregnancy	0.71 (0.61, 0.83)	0.49 (0.44, 0.55)	1.27 (1.18, 1.37)	1.48 (1.29, 1.71)	0.17 (0.14, 0.20)	0.26 (0.23, 0.29)	0.19 (0.16, 0.22)
Growth in early-third trimester	0.81 (0.64, 1.02)	0.68 (0.55, 0.85)	1.27 (1.14, 1.43)	1.20 (0.93, 1.57)	0.14 (0.10, 0.18)	0.20 (0.16, 0.24)	0.14 (0.09, 0.19)
Growth in late-third trimester	0.82 (0.71, 0.94)	0.75 (0.65, 0.86)	1.09 (1.01, 1.19)	1.02 (0.83, 1.26)	0.12 (0.09, 0.15)	0.12 (0.09, 0.16)	0.06 (0.02, 0.09)

All models were adjusted for maternal age, education level, monthly income, pre-pregnancy body mass index, parity, active or passive smoking during pregnancy, diabetes during pregnancy, and breastfeeding duration. Models for early-third trimester were additionally adjusted for growth in mid-pregnancy; models for late-third trimester were additionally adjusted for growths in mid-pregnancy and early-third trimester.

Table S11. Association between foetal growth Z scores and child growth outcomes using WHO growth standard

Fetal growth variables	Risk ratio (95% confidence interval)				Regression coefficients (95% confidence interval)		
	Stunting	Underweight	At risk of overweight	Overweight/obesity	Length/height-for-age Z score	Weight-for-age Z score	BMI-for-age Z score
Size in early pregnancy	0.65 (0.55, 0.78)	0.49 (0.39, 0.60)	1.23 (1.15, 1.32)	1.42 (1.23, 1.65)	0.19 (0.16, 0.21)	0.23 (0.21, 0.26)	0.17 (0.14, 0.20)
Growth in mid-pregnancy	0.65 (0.55, 0.77)	0.49 (0.40, 0.60)	1.24 (1.16, 1.33)	1.45 (1.24, 1.68)	0.19 (0.16, 0.21)	0.23 (0.21, 0.26)	0.18 (0.15, 0.21)
Growth in early-third trimester	0.85 (0.66, 1.10)	0.66 (0.43, 1.01)	1.26 (1.13, 1.40)	1.26 (0.96, 1.66)	0.15 (0.11, 0.19)	0.18 (0.14, 0.22)	0.13 (0.09, 0.18)
Growth in late-third trimester	0.81 (0.69, 0.97)	0.71 (0.58, 0.87)	1.08 (1.00, 1.17)	1.07 (0.87, 1.32)	0.13 (0.10, 0.16)	0.12 (0.09, 0.15)	0.05 (0.02, 0.09)

All models were adjusted for maternal age, education level, monthly income, pre-pregnancy body mass index, parity, active or passive smoking during pregnancy, diabetes during pregnancy, hypertensive disorders during pregnancy, and breastfeeding duration. Models for early-third trimester were additionally adjusted for growth in mid-pregnancy; models for late-third trimester were additionally adjusted for growths in mid-pregnancy and early-third trimester.

Table S12. Comparison of baseline characteristics of participants with and without ultrasound data for 22-27 weeks

Variables	Women with ultrasound data	
	Yes, n=2,710	No, n=2,108
Maternal age (years), mean (SD)	29.4 (3.4)	29.1 (3.1)
Educational level (%)		
Middle school or below	8.0	6.2
Vocational or technical college	25.1	23.3
Undergraduate	53.7	58.8
Postgraduate	13.1	11.7
Monthly income (Yuan) (%)		
≤1500	10.4	8.4
1501-4500	26.7	33.6
4501-9000	46.1	42.2
≥9001	16.8	15.8
Pre-pregnancy BMI (kg/m ²), mean (SD)	20.3 (2.6)	20.5 (2.6)
Nulliparous (%)	86.3	90.7
Diabetes during pregnancy (%)	13.7	12.6
Hypertensive disorder in pregnancy (%)	2.8	2.5
Active/passive smoking during pregnancy (%)	28.6	30.8
Breastfeeding duration, months, mean (SD)	8.3 (3.8)	8.5 (3.7)

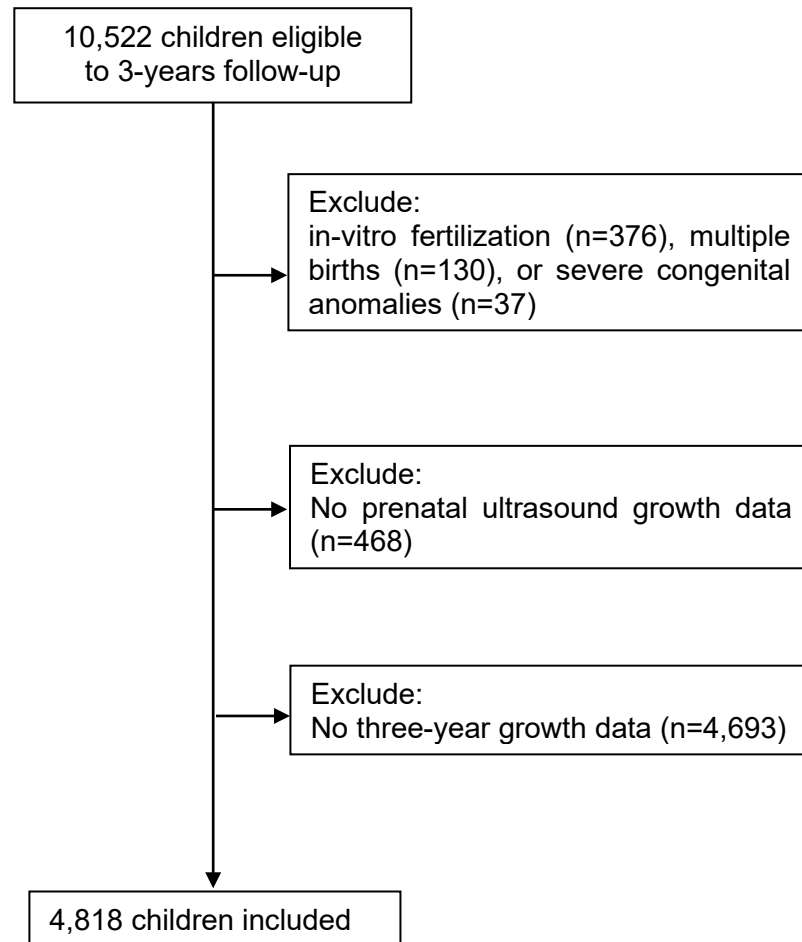


Figure S1. Flowchart of participant inclusion

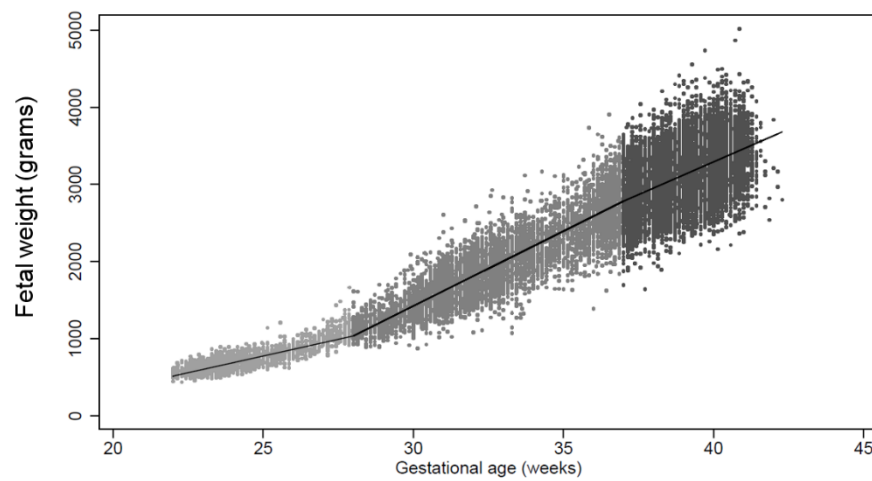


Figure S2. Linear splines for fetal growth trajectories. Light-grey dots represent the observed fetal weight or birth weight at 22-27 weeks, moderate-grey dots for 28-36 weeks, and dark-grey dots for 37 weeks or above. Black line represents the linear splines.

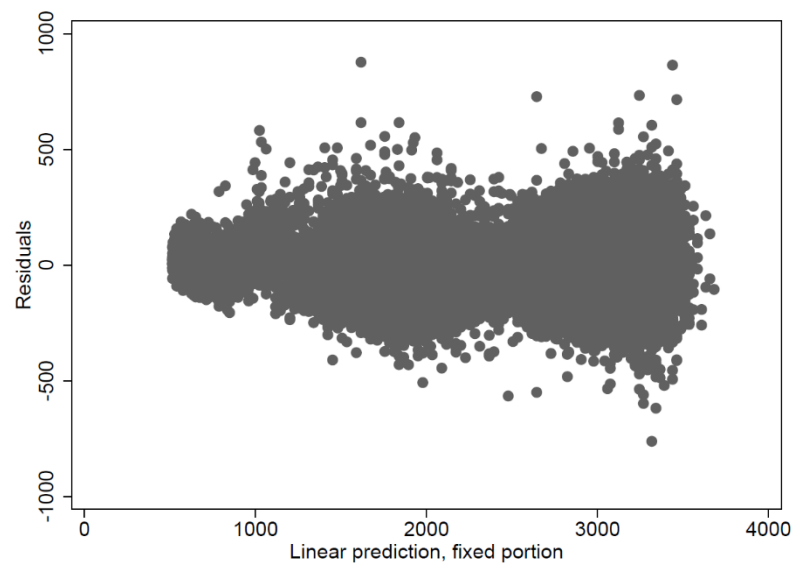


Figure S3. Residuals plots for the multilevel linear model

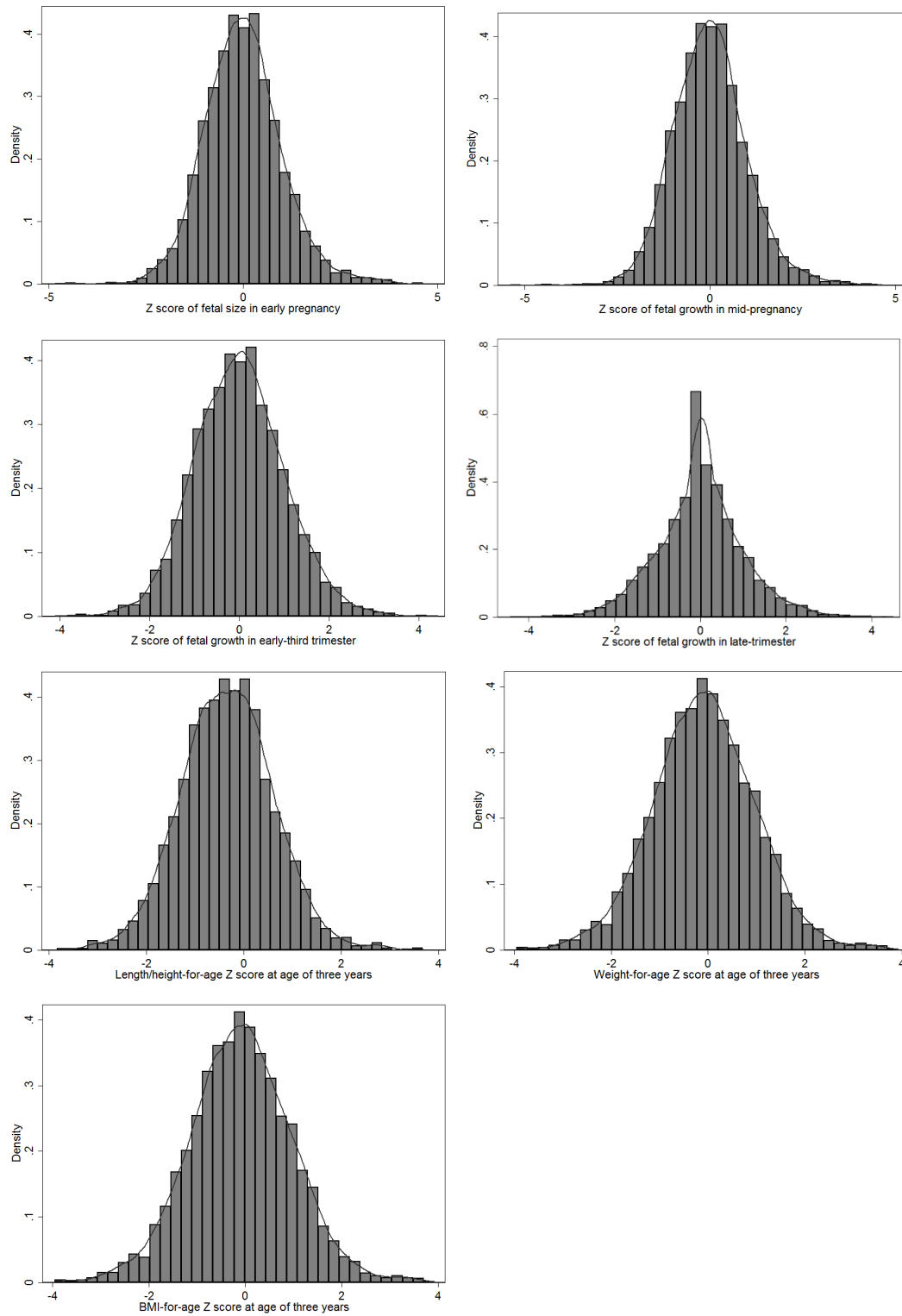


Figure S4. Distributions of fetal growth Z scores in each period and child growth Z scores at the age of three years.

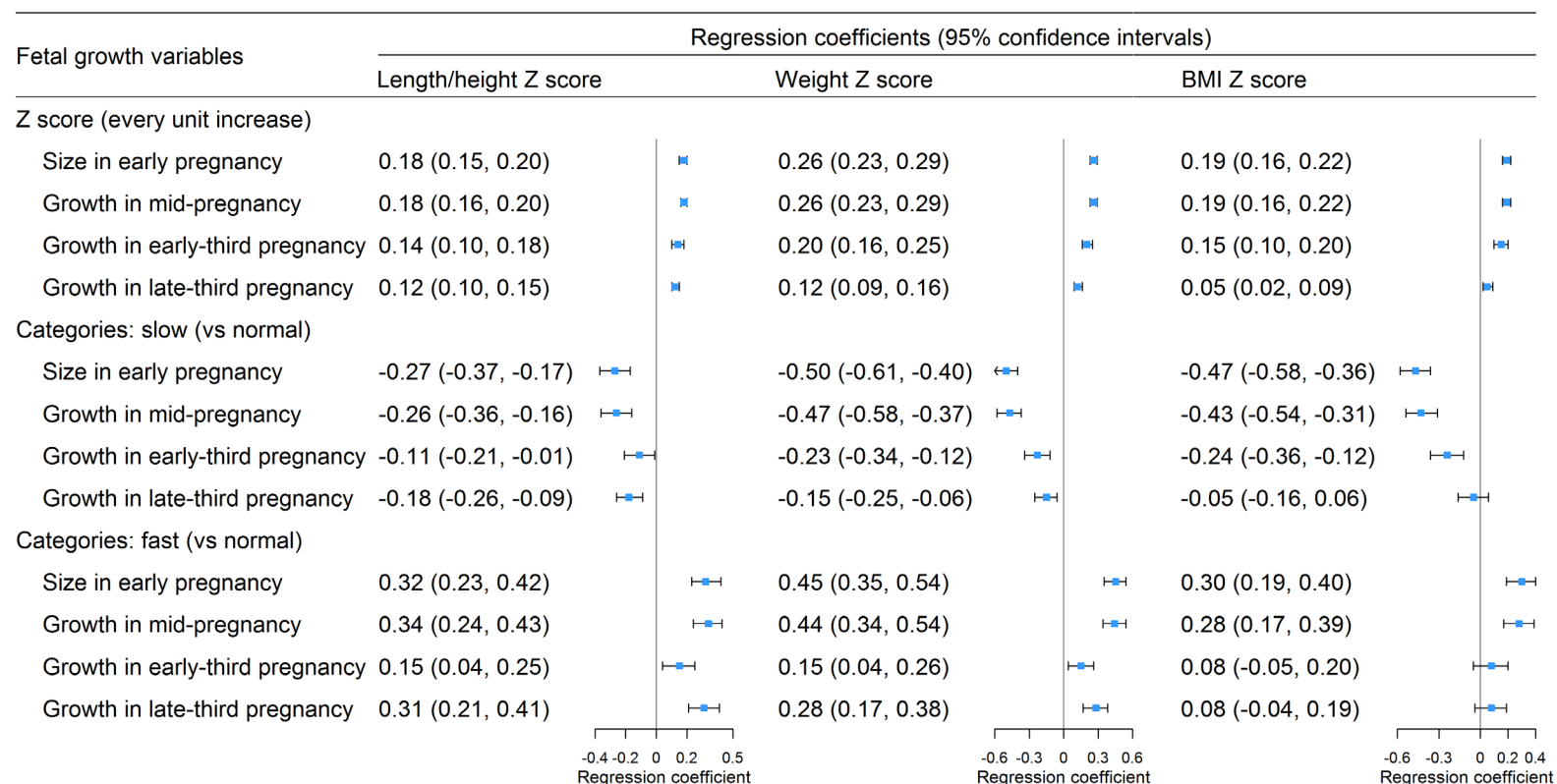


Figure S5. Associations between fetal growth variables at different gestational periods and continuous child growth outcomes.

Early pregnancy refers to 22 weeks; mid-pregnancy, 22-27 weeks; early-third trimester, 28-36 weeks; late-third trimester, 37 weeks and above. Slow, normal, and fast growths were defined as Z score < -1.28 , -1.28 to 1.28 , and > 1.28 , respectively. All models were adjusted for maternal age, education level, monthly income, pre-pregnancy body mass index, parity, active or passive smoking during pregnancy, diabetes during pregnancy, hypertensive disorders during pregnancy, and breastfeeding duration. Models for early-third trimester were additionally adjusted for growth in mid-pregnancy; models for late-third trimester were additionally adjusted for growths in mid-pregnancy and early-third trimester.

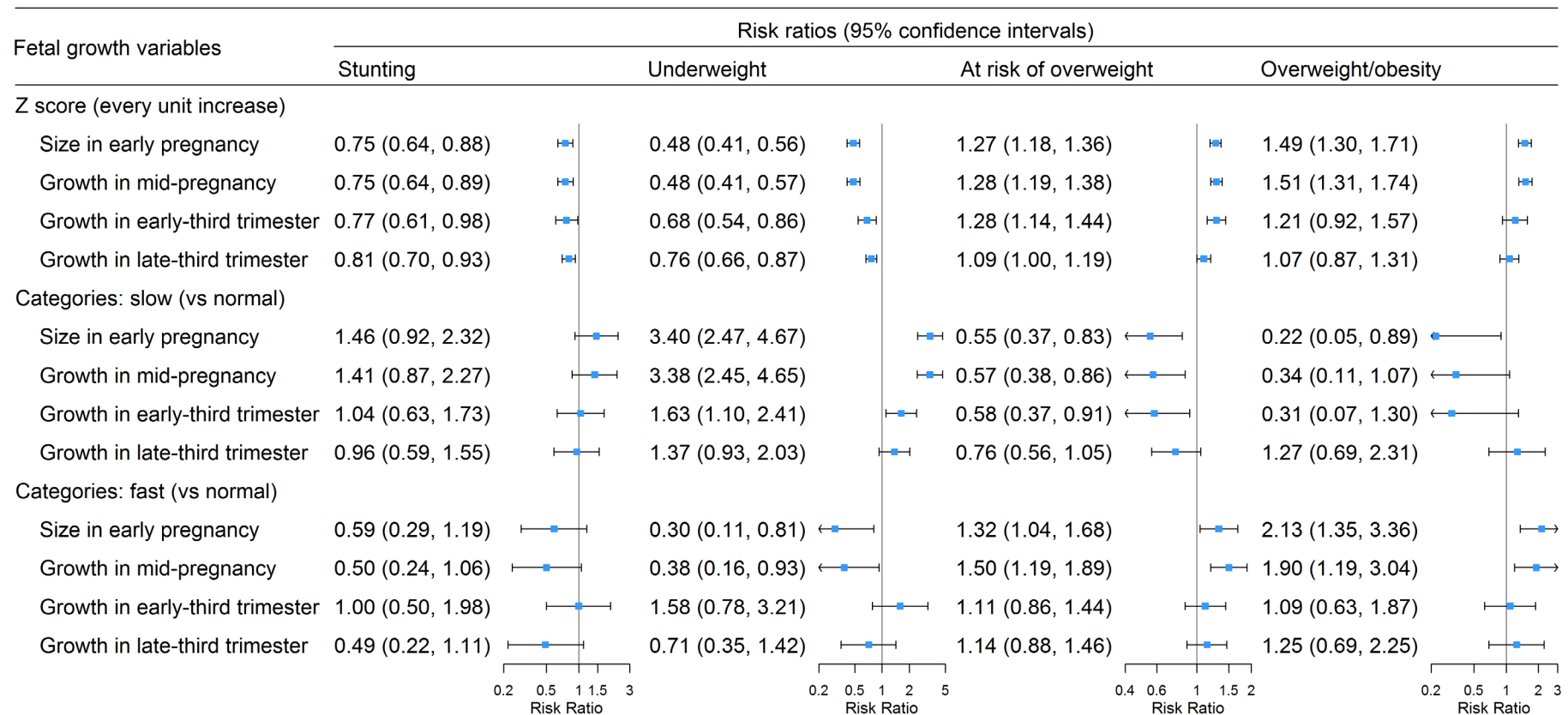


Figure S6. Associations between fetal growth variables at each period and categorized child growth outcomes among children born at term. Early pregnancy refers to 22 weeks; mid-pregnancy, 22-27 weeks; early-third trimester, 28-36 weeks; late-third trimester, 37 weeks and above. Slow, normal, and fast growths were defined as Z score < -1.28, -1.28 to 1.28, >1.28, respectively. All models were adjusted for maternal age, education level, monthly income, pre-pregnancy body mass index, parity, active or passive smoking during pregnancy, diabetes during pregnancy, hypertensive disorders during pregnancy, and breastfeeding duration. Models for early-third trimester were additionally adjusted for growth in mid-pregnancy; models for late-third trimester were additionally adjusted for growths in mid-pregnancy and early-third trimester.