The association of fetal growth rate and growth in first year of life with childhood overweight: A cohort study Supplementary

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Directed acyclic graph

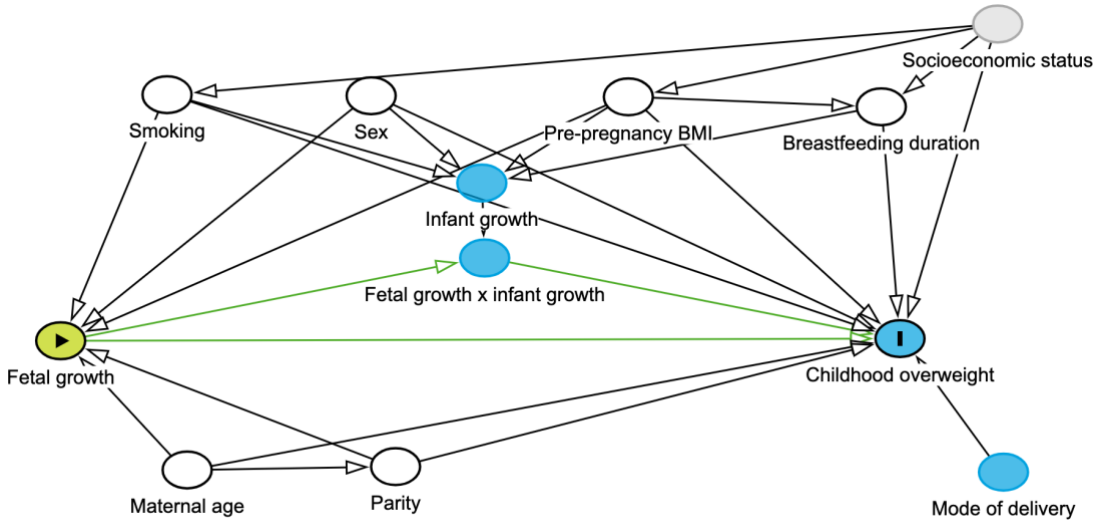

Figure S1: Directed acyclic graph of the association between fetal and infant growth and later overweight.

Characteristics based on ultrasound scans

	No. ultrasound scans	
Characteristic	**Extra**, N = 2,882	**Routine**, N = 3,324
Maternal age (years), Mean (SD)	31 (5)	30 (5)
Pre-pregnancy weight (kg), Mean (SD)	68 (15)	66 (12)
Height (cm), Mean (SD)	168 (7)	168 (6)
BMI (kg/m^2), Mean (SD)	23.9 (4.8)	23.3 (4.1)
Smoking, n (%)	176 (6.1)	187 (5.7)
Ethnicity, n (%)		
Caucasian	2,576 (90)	3,036 (92)
Other	276 (9.7)	263 (8.0)
Parity (nullipara), n (%)	1,052 (42)	1,379 (49)
Diabetes, n (%)		
No diabetes	2,647 (92)	3,310 (100)
GDM	211 (7.3)	14 (0.4)
T2DM	12 (0.4)	0 (0)
T1DM	12 (0.4)	0 (0)
Maternal education, n (%)		
No education	16 (2.3)	7 (0.8)
Primary school	131 (19)	133 (15)
High school	130 (19)	199 (23)
Higher education	405 (59)	529 (61)
Cesarean section, n (%)	587 (21)	455 (14)
Fetal growth rate in week 34 (g/week), Mean (SD)	203 (31)	205 (26)
Birthweight (g), Mean (SD)	3,503 (493)	3,575 (439)
Birthweight Z-score, Mean (SD)	-0.19 (1.06)	-0.08 (0.92)
Size at birth, n (%)		
AGA	2,233 (77)	2,793 (84)
SGA	410 (14)	289 (8.7)
LGA	239 (8.3)	242 (7.3)
AC Z-score week 19-25, Mean (SD)	0.34 (0.86)	0.39 (0.82)
HC Z-score week 19-25, Mean (SD)	-0.27 (0.61)	-0.21 (0.61)
FL Z-score week 19-25, Mean (SD)	-0.35 (0.63)	-0.31 (0.61)
Sex (boy), n (%)	1,411 (49)	1,669 (50)
Gestational age (days), Mean (SD)	281 (9)	281 (8)
No. of ultrasound scans, Mean (SD)	2.93 (1.27)	1.00 (0.00)
Breastfeeding duration, n (%)		
No breastfeeding	402 (16)	386 (14)
0-4 months	498 (20)	513 (19)
≥ 4 months	1,537 (63)	1,846 (67)
Overweight in childhood, n (%)	524 (18)	556 (17)
BMI-for-age Z-score at 4-9 years, Mean (SD)	0.14 (1.02)	0.09 (1.00)
Age at BMI measurement (years), Mean (SD)	7.11 (0.71)	7.20 (0.68)

Table S1. Characteristics of those receiving routine ultrasound care and those receiving additional scans. Z-scores of birthweight calculated using Marsal[1]. AGA: Appropriate for gestational age, SGA: Small for gestational age (<10th percentile), LGA: Large for gestational age (>90th percentile).

Fetal growth trajectory

Cubic mixed model of fetal growth.

```
df$ga2 <- ga^2
df$ga3 <- ga^3

trajectory <- nlme::lme(efw~ga+ga2+ga3,
                  data=df,
                  random=~ga+ga2|child_id,
                  na.action=na.exclude,
                  control = lmeControl(opt='optim'))
```

To estimate trajectories of abdominal circumference, head circumference, and femur length, we created mixed model regressions. Abdominal circumference and head circumference at birth was used in continuation of ultrasound estimates, if available. A minimum of two measurements, either using ultrasound examination or at birth, were required. The data was restricted to those having two measures of all three variables. See below for model specifications.

```
# ga = gestational age
data$ga2 <- data$ga^2
data$ga3 <- data$ga^3

# Abdominal circumference
trajectory_abdominal_circumference <-
        lme(abdominal_circumference~ga+ga2+ga3,
                        data=data,
                        random=~ga|id,
                        na.action=na.exclude,
                        control = lmeControl(opt='optim'))

# Head circumference
trajectory_head_circumference <-
        lme(head_circumference~ga+ga2+ga3,
                        data=data,
                        random=~ga|id,
                        na.action=na.exclude,
                        control = lmeControl(opt='optim'))

# Femur length
trajectory_femur_length <-
        lme(femur_length~ga+ga2+ga3*weight_status,
                        data=data,
                        random=~ga|id,
                        na.action=na.exclude,
                        control = lmeControl(opt='optim'))
```

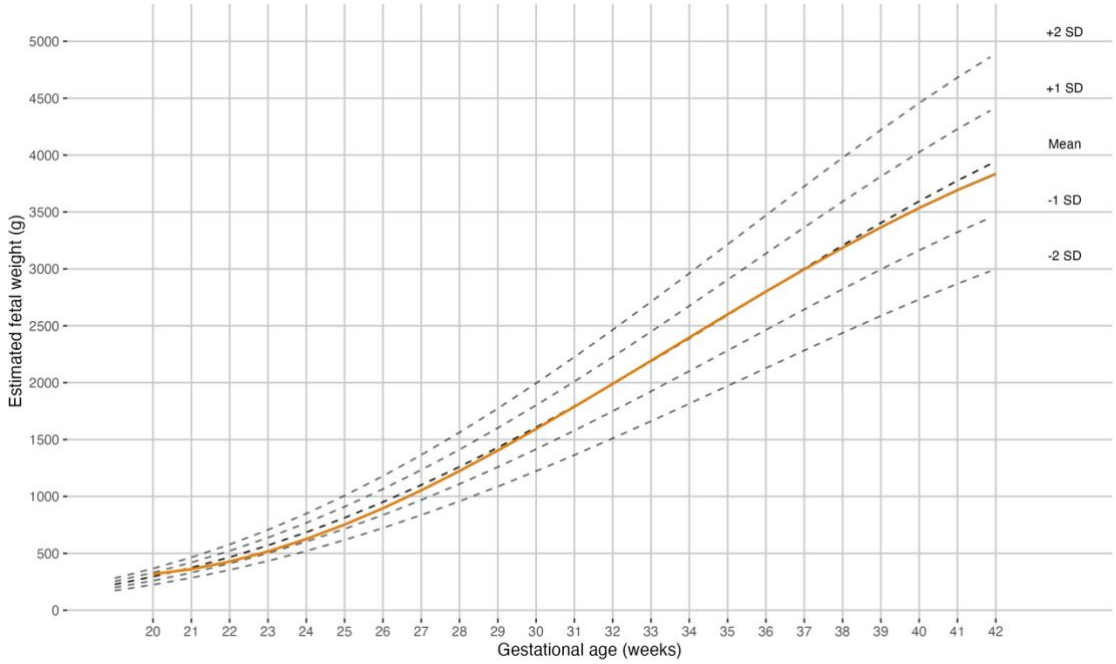

Figure S2: Fetal growth trajectory. Dashed lines shows mean +/- 2SD using a Scandinavian reference material[19]

Infant growth

Latent class growth mixture model of infant growth using mixed model cubic splines. We optimized the model using a grid search with 20 repetitions with a maximum of 100 iterations each. See below.

```
# 1 group to initiate
lcgmm_spline_1 <-
        lcmm::hlme(zbmi ~ Epi::Ns(age, knots = c(0.3, 50, 100, 363)),
             subject = "id",
             random = ~1,
             ng = 1,
             data = Data)

# Gridsearch solution - 3 classes
lcgmm_spline_3_z_grid <-
        lcmm::gridsearch(rep = 20, maxiter = 100, minit = lcgmm_spline_1,
                    hlme(zbmi ~ Epi::Ns(age, knots = c(0.3, 50, 100, 363))
,
                         subject = "id",
                         random = ~1,
                         mixture =  ~ Ns(age, knots = c(0.3, 50, 100, 363)
),
                         ng = 3,
                         data = Data))
```

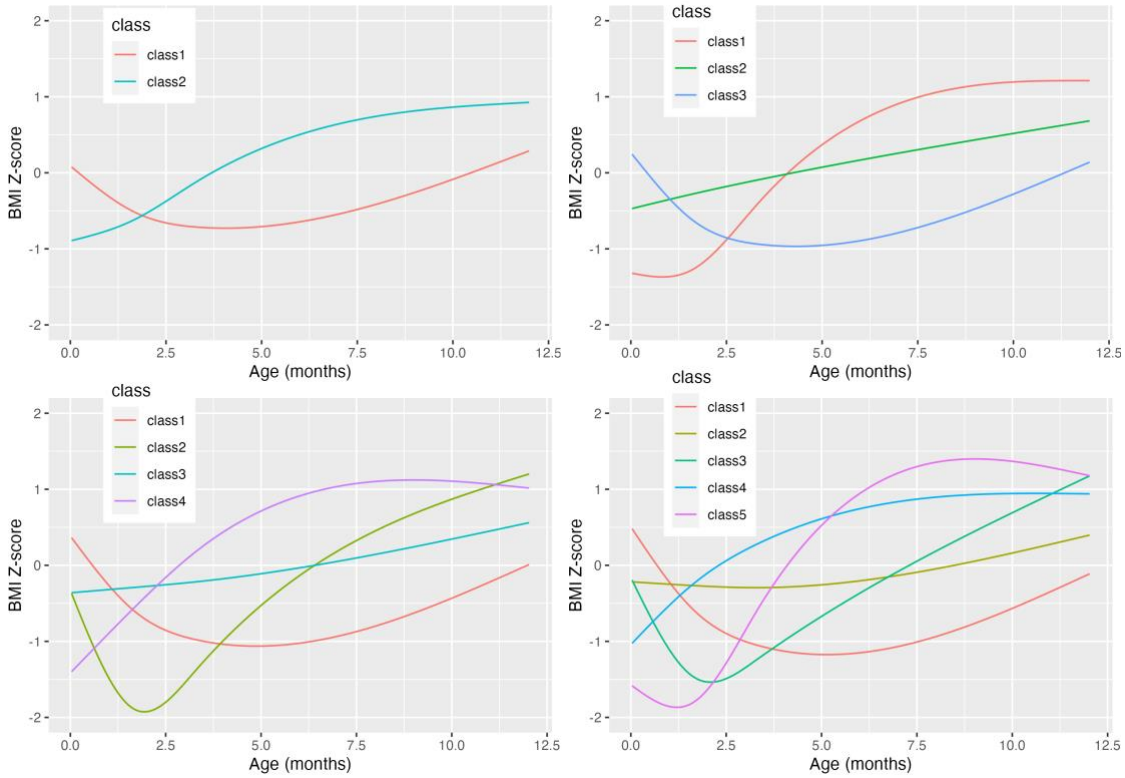

Figure S3. Trajectories of the 2-5 group solutions of BMI-z trajectories in infancy.

Posterior probabilities

No. of groups	Group	Proportion (%)	Mean posterior probability of assignment (%)					Relative entropy (%)	BIC	AIC
			1	2	3	4	5			
2	1	63	89	11				61	461128.18	461034.85
	2	37	14	86						
3	1	9	82	17	1			61	434161.1	434025.9
	2	51	7	79	14					
	3	40	0.4	16	84					
4	1	27	81	2	17	0		65	450175.89	449997.7
	2	6	5	77	13	6				
	3	55	12	3	79	6				
	4	12	0	4	15	81				
5	1	19	78	17	4	0	0	63	427076.12	426856.41
	2	51	10	75	7	8	0			
	3	10	5	15	71	6	3			
	4	18	0	15	4	77	4			
	5	3	0	1	7	13	79			

Table S2. Posterior probabilities, relative entropy, Bayesian information criterion (BIC) and Akaike information criterion (AIC) for 2-5 group solutions.

Fetal growth in week 28 and infant growth and later overweight

		Infant growth	
Fetal growth	Average	Accelerated	Decelerated
Unadjusted			
Average	Reference, n = 1738	1.79 (1.34-2.4), n =240	0.44 (0.36-0.54), n =1549
Slow	0.64 (0.52-0.8), n =877	0.97 (0.67-1.39), n =194	0.28 (0.2-0.41), n =507
Fast	1.63 (1.3-2.04), n =473	3.72 (1.88-7.36), n =34	0.78 (0.61-0.99), n =594
Adjusted			
Average	Reference, n = 1738	1.69 (1.24-2.3), n =240	0.46 (0.37-0.56), n =1549
Slow	0.67 (0.53-0.84), n =877	0.99 (0.68-1.45), n =194	0.31 (0.22-0.45), n =507
Fast	1.44 (1.14-1.83), n =473	2.85 (1.4-5.81), n =34	0.74 (0.58-0.95), n =594

Table S3. Table 3**.** Odds ratios (95% CI) of overweight in the different combinations of fetal growth groups in week 28 (slow: ≤164 g/week, average: 165-189 g/week, fast: ≥190 g/week) and infant growth group (average, decelerated, and accelerated). Unadjusted and adjusted for maternal pre-pregnancy BMI, age, parity, smoking, and breastfeeding duration. OR: Odds ratio, CI: Confidence interval.

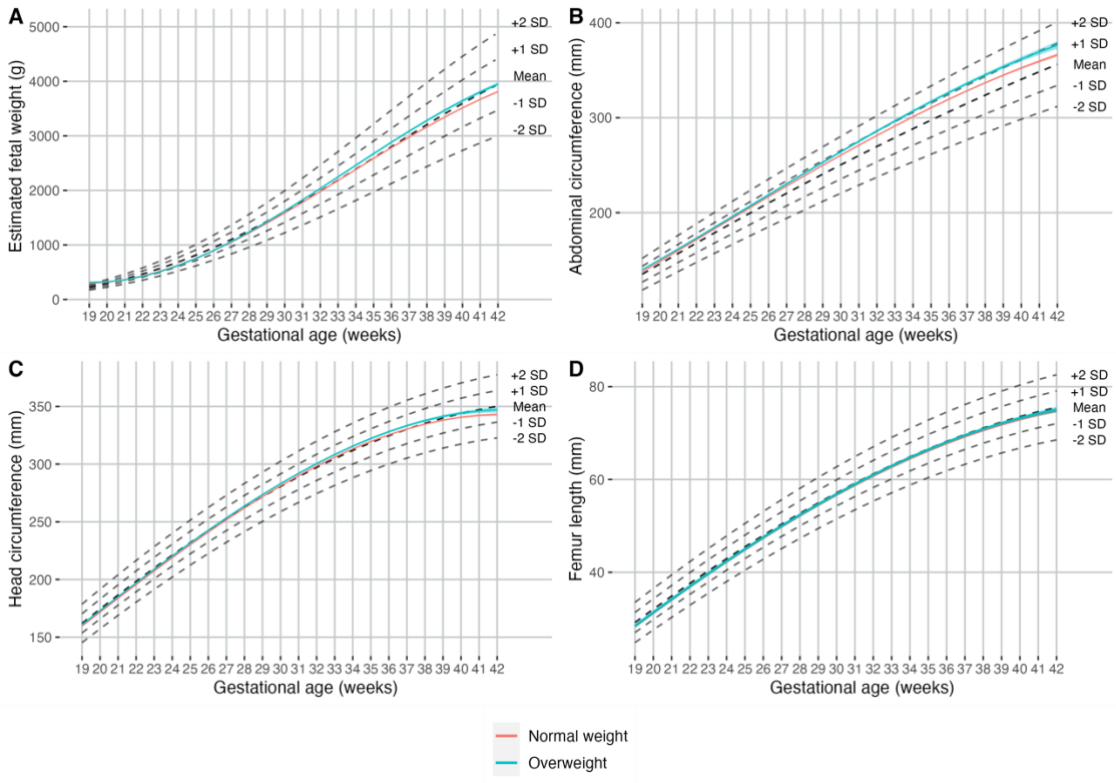

Figure S4: Trajectories of A: Estimated fetal weight, B: Abdominal circumference, C: Head circumference, and D: Femur length from 19 to 42 weeks of gestation in children with overweight (orange line) and normal weight (blue line) at 5-9 years of age. The colored ribbons around the lines show 95% confidence interval for the model derived estimates. The shaded area shows the 2.5th to 97.5th centile range of data. Dashed lines show mean +/- 2 SD using the formula by Marsal[1] et al for estimated fetal weight and the formulas by Chitty et al for abdominal[2] and head[3] circumference and femur length[4].

Supplementary references

1. Marsál, K. *et al*. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr* **85**, 843–8 (1996).
2. Chitty, L. S., Altman, D. G., Henderson, A. & Campbell, S. Charts of fetal size: 3. Abdominal measurements. *BJOG: An International Journal of Obstetrics & Gynaecology* **101**, 125–131 (1994).
3. Chitty, L. S., Altman, D. G., Henderson, A. & Campbell, S. Charts of fetal size: 2. Head measurements*. *BJOG: An International Journal of Obstetrics & Gynaecology* **101**, 35–43 (1994).
4. Chitty, L. S., Altman, D. G., Henderson, A. & Campbell, S. Charts of fetal size: 4. Femur length. *BJOG: An International Journal of Obstetrics & Gynaecology* **101**, 132–135 (1994).