Body mass index trajectories in early childhood in relation to cardiometabolic risk profile and body composition at 5 years of age

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Supplemental Tables

Supplemental Table 1

Supplemental Table 1 Description of the mother-child pairs attending the 5-year follow-up visit and included in the trajectory modelling (n= 352)

	Full sample [1]	Missing, n
Maternal characteristics		
Age at birth, years	24.6 (4.7)	0
Height, cm	157.1 (6.1)	2
Body mass index, kg/m^2	22.23 (3.52)	6
Birth order of current child		
First	49.4	
Second	26.3	
Third or above	24.3	6
Breastfeeding status at 4 to 6 months post-partum		
Exclusive	12.3	
Almost exclusive, water given	21.4	
Predominant	60.2	
Partial or no	6.0	20
Maternal education		
No school	7.1	
Some primary school	44.6	
Completed primary school	15.6	
Completed secondary school	19.6	
Higher education	13.1	0
Socioeconomic status, International Wealth Index	45.6 (17.1)	0
Child characteristics at birth		
Sex, boys	50.3	0
Gestational age, weeks	39.0 (1.0)	0
Weight, kg	3.04 (0.41)	0
Length, cm	49.1 (2.0)	0
Fat mass, kg	0.22 (0.16)	2
Fat free mass, kg	2.83 (0.32)	2
Low birth weight, %	9.4	0
Child characteristics at 5 years		
Age at 5-year visit, months	59.9 (1.5)	0
Weight, kg	16.32 (2.08)	0
Length, cm	104.2 (4.4)	0
Weight for age z score [2]	-0.88 (0.88)	0
Height for age z score	-1.16 (0.91)	0
BMI for age z score	-0.23 (0.87)	0
Underweight [3]	9.4	0
Stunted [4]	15.3	0
Wasted by BMI, Thinness [5]	2.8	0
Overweight [6]	4.8	0
Obese [7]	1.1	0

[1] Data are mean (SD) for continuous normally distributed variables and percentages for categorical variables. [2] z scores are derived using the 2006 (aged <61 months) and 2007 (aged ≥61 months) World Health Organization (WHO) child growth standards. [3] Weight for age more than 2 SDs below the age- and sex-specific median of the WHO child growth standards. [4] Height for age more than 2 SDs below the age- and sex-specific median of the WHO child growth standards. [5] BMI for age more than 2 SDs below the age- and sex-specific median of the WHO child growth standards. [6] BMI-for-age from 1 to 2 SDs above the age- and sex-specific median of the WHO child growth standards. [7] BMI-for-age more than 2 SDs above the age- and sex-specific median of the WHO child growth standards.

Supplemental Table 2

Supplemental Table 2 Cardiometabolic markers and body composition at 5 years of age in the children attending the 5-year follow-up visit and included in the trajectory modelling (n= 352)

	Full sample [1]	Missing, n
Glucose metabolism		
Glucose, mmol/L	5.90 (0.84)	26
HbA1c, mmol/mol	38 (4)	83
Insulin, µU/mL [2]	5.94 (3.20, 11.12)	34
C-peptide, ng/mL [2]	1.06 (0.65, 1.53)	39
HOMA-IR [2,3]	1.28 (0.65, 2.46)	34
Lipids		
Total cholesterol, mmol/L	3.41 (0.61)	30
LDL, mmol/L	1.65 (0.56)	31
HDL, mmol/L	0.79 (0.26)	35
Triglycerides, mmol/L [2]	0.95 (0.73, 1.28)	35
Blood pressure		
Systolic, mmHg	87.8 (7.3)	2
Diastolic, mmHg	54.3 (8.5)	2
Anthropometry and body composition		
Body mass index, kg/m^2	14.99 (1.22)	0
Waist circumference, cm	51.45 (3.01)	1
Fat mass, kg	4.17 (1.27)	16
Fat-free mass, kg	12.16 (1.42)	16
Fat mass, %	25.2 (5.9)	16
Fat-free mass, %	74.8 (5.9)	16
Fat mass index, kg/m^2	3.82 (1.07)	16
Fat-free mass index, kg/m^2	11.19 (0.86)	16

[1] Data are mean (SD) for continuous normally distributed variables and median (interquartile range, IQR) for continuous nonnormally distributed variables. Variables found not to follow a normal distribution were log transformed prior to the tests of group differences. [2] Nonnormally distributed. [3] Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as insulin (µU/mL) × glucose (mmol/l) / 22.5.

Supplemental Table 3

Supplemental Table 3 Comparison of background characteristics of the mother-child pairs attending the 5-year follow-up visit with those not attending [1]

	Full sample (n = 632)	**Not attending the visit at 5 years** (n = 280)	**Attending the visit at 5 years** (n = 352)	***p*-value [2]**	**Missing, n**
Maternal characteristics					
Age at birth, years	24.15 (4.61)	23.6 (4.39)	24.56 (4.74)	0.010	11
Postpartum height, cm	157.52 (5.96)	158.16 (5.76)	157.07 (6.07)	0.028	37
Postpartum body mass index, kg/m^2	22.28 (3.43)	22.39 (3.25)	22.23 (3.52)	0.596	105
Birth order of current child					
First	55.2	62.4	49.7		
Second	23.9	20.7	26.4		
Third or above	20.9	17	23.9	0.007	9
Breastfeeding status at 4 to 6 months post-partum					
Exclusive	14.3	18.4	12.3		
Almost exclusive, water given	22.7	25.7	21.4		
Predominant	57.6	52	60.2		
Partial or no	5.4	3.9	6	0.132	148
Maternal education					
No school	7	6.9	7.1		
Some primary school	45.5	46.7	44.6		
Completed primary school	15.2	14.6	15.6		
Completed secondary school	18.4	16.8	19.6		
Higher education	13.9	15	13.1	0.857	6
Socioeconomic status, International Wealth Index	45.73 (18.21)	45.95 (19.66)	45.56 (17.06)	0.795	13
Child characteristics at birth					
Gender, female	50.6	51.8	49.7	0.662	0
Gestational age, weeks	39.03 (0.95)	39.03 (0.96)	39.03 (0.95)	0.954	0
Weight, kg	3.03 (0.42)	3.02 (0.42)	3.04 (0.41)	0.407	0
Length, cm	49.1 (2)	49.07 (2.02)	49.12 (1.98)	0.751	0
Fat mass, kg	0.22 (0.16)	0.21 (0.15)	0.22 (0.16)	0.599	3
Fat-free mass, kg	2.82 (0.33)	2.8 (0.35)	2.83 (0.32)	0.405	3
Low birth weight, % [3]	10	10.7	9.4	0.671	0

[1] Data are mean (SD) for continuous normally distributed variables and percentages for categorical variables. [2] Differences between groups were calculated by One-way ANOVA F-test for continuous variables and Pearson's Chi-Square test of independence for categorical variables. [3] Low birth weight is defined as birth weight <2500 g.

Supplemental Table 4

Supplemental Table 4 Associations of distinct body mass index (BMI) trajectories from 0-5 years with cardiometabolic markers and body composition at 5 years [1]

		1: Stable low BMI				3: Rapid catch-up to high BMI				4: Slow catch-up to high BMI			
	n	β	95% CI		p-value	β	95% CI		p-value	β	95% CI		p-value
Glucose, mmol/L	324												
Model 1		-0.04	-0.28	0.20	0.733	0.07	-0.20	0.34	0.615	-0.03	-0.31	0.24	0.810
Model 2		-0.04	-0.28	0.20	0.722	0.07	-0.20	0.35	0.591	-0.04	-0.32	0.25	0.791
Model 3		-0.04	-0.29	0.20	0.719	0.08	-0.19	0.35	0.566	-0.04	-0.32	0.25	0.812
Model 4		-0.04	-0.29	0.21	0.759	0.07	-0.21	0.36	0.603	-0.04	-0.33	0.25	0.790
HbA1c, mmol/mol	267												
Model 1		-0.1	-1.4	1.2	0.878	0.8	-0.7	2.4	0.296	-0.2	-1.8	1.3	0.776
Model 2		-0.3	-1.6	1.1	0.679	0.7	-0.9	2.2	0.406	-0.2	-1.8	1.4	0.802
Model 3		-0.3	-1.6	1.1	0.683	0.7	-0.9	2.2	0.413	-0.2	-1.8	1.4	0.801
Model 4		-0.5	-1.9	0.9	0.522	0.8	-0.8	2.4	0.329	-0.0	-1.7	1.6	0.961
Insulin, % change	316												
Model 1		-10.6	-31.7	17.2	0.417	32.4	-2.7	80.1	0.074	6.5	-22.5	46.2	0.698
Model 2		-8.8	-30.5	19.8	0.509	29.3	-5.2	76.5	0.104	3.3	-25.0	42.3	0.840
Model 3		-8.7	-30.5	19.9	0.512	28.7	-6.0	76.3	0.115	3.1	-25.2	42.2	0.852
Model 4		-3.3	-27.0	28.0	0.814	22.5	-11.0	68.5	0.212	-1.8	-29.1	36.0	0.911
C-peptide, % change	311												
Model 1		-7.4	-23.2	11.5	0.414	25.0	1.1	54.7	0.040	2.5	-17.7	27.6	0.827
Model 2		-6.2	-22.3	13.3	0.505	24.9	0.7	54.9	0.043	2.5	-17.9	28.0	0.825
Model 3		-6.0	-22.1	13.4	0.517	22.8	-1.2	52.6	0.064	1.7	-18.6	27.0	0.884
Model 4		-6.1	-22.7	14.0	0.522	22.9	-1.5	53.4	0.067	1.8	-18.9	27.7	0.878
HOMA-IR, % change [2]	316												
Model 1		-12.4	-34.3	16.8	0.366	31.7	-5.2	82.9	0.100	6.8	-23.9	49.9	0.702
Model 2		-10.3	-32.9	20.0	0.463	28.3	-7.9	78.8	0.140	3.6	-26.4	45.7	0.840
Model 3		-10.2	-32.9	20.1	0.467	27.5	-8.8	78.4	0.155	3.2	-26.7	45.5	0.856
Model 4		-5.1	-29.7	28.0	0.731	21.5	-13.6	70.9	0.261	-1.5	-30.5	39.4	0.930
Total cholesterol, mmol/L	320												
Model 1		-0.12	-0.29	0.06	0.191	0.07	-0.12	0.27	0.466	-0.05	-0.25	0.16	0.649
Model 2		-0.13	-0.31	0.04	0.129	0.04	-0.16	0.24	0.678	-0.07	-0.27	0.14	0.521
Model 3		-0.14	-0.31	0.04	0.127	0.05	-0.15	0.25	0.628	-0.06	-0.27	0.14	0.547
Model 4		-0.14	-0.32	0.04	0.120	0.06	-0.15	0.26	0.594	-0.06	-0.26	0.15	0.593
LDL, mmol/L	319												
Model 1		-0.14	-0.30	0.02	0.087	0.03	-0.16	0.21	0.772	-0.03	-0.22	0.16	0.760
Model 2		-0.16	-0.32	-0.00	0.046	0.01	-0.17	0.19	0.921	-0.05	-0.24	0.14	0.611
Model 3		-0.16	-0.32	-0.00	0.045	0.02	-0.17	0.20	0.854	-0.04	-0.23	0.14	0.643
Model 4		-0.17	-0.33	-0.00	0.048	0.02	-0.17	0.21	0.832	-0.04	-0.23	0.15	0.671
HDL, mmol/L	315												
Model 1		-0.05	-0.13	0.02	0.154	-0.05	-0.13	0.04	0.285	-0.03	-0.12	0.06	0.490
Model 2		-0.08	-0.15	-0.00	0.042	-0.06	-0.14	0.02	0.157	-0.04	-0.12	0.05	0.382
Model 3		-0.08	-0.15	-0.00	0.042	-0.06	-0.14	0.02	0.169	-0.04	-0.12	0.05	0.390
Model 4		-0.09	-0.16	-0.01	0.020	-0.05	-0.13	0.04	0.276	-0.03	-0.11	0.06	0.556
Triglycerides, % change	315												
Model 1		10.5	-1.9	24.4	0.100	20.2	5.1	37.5	0.007	2.6	-10.7	17.8	0.717
Model 2		11.6	-0.9	25.8	0.071	21.4	6.1	39.0	0.005	1.4	-11.8	16.6	0.842
Model 3		11.7	-0.9	25.9	0.070	20.5	5.1	38.1	0.008	1.0	-12.1	16.1	0.887
Model 4		13.2	0.0	28.0	0.050	19.1	3.7	36.9	0.014	-0.1	-13.3	15.1	0.988

Table continues on the next page.

Supplemental Table 4 (continued) Associations of distinct body mass index (BMI) trajectories from 0-5 years with cardiometabolic markers and body composition at 5 years [1]

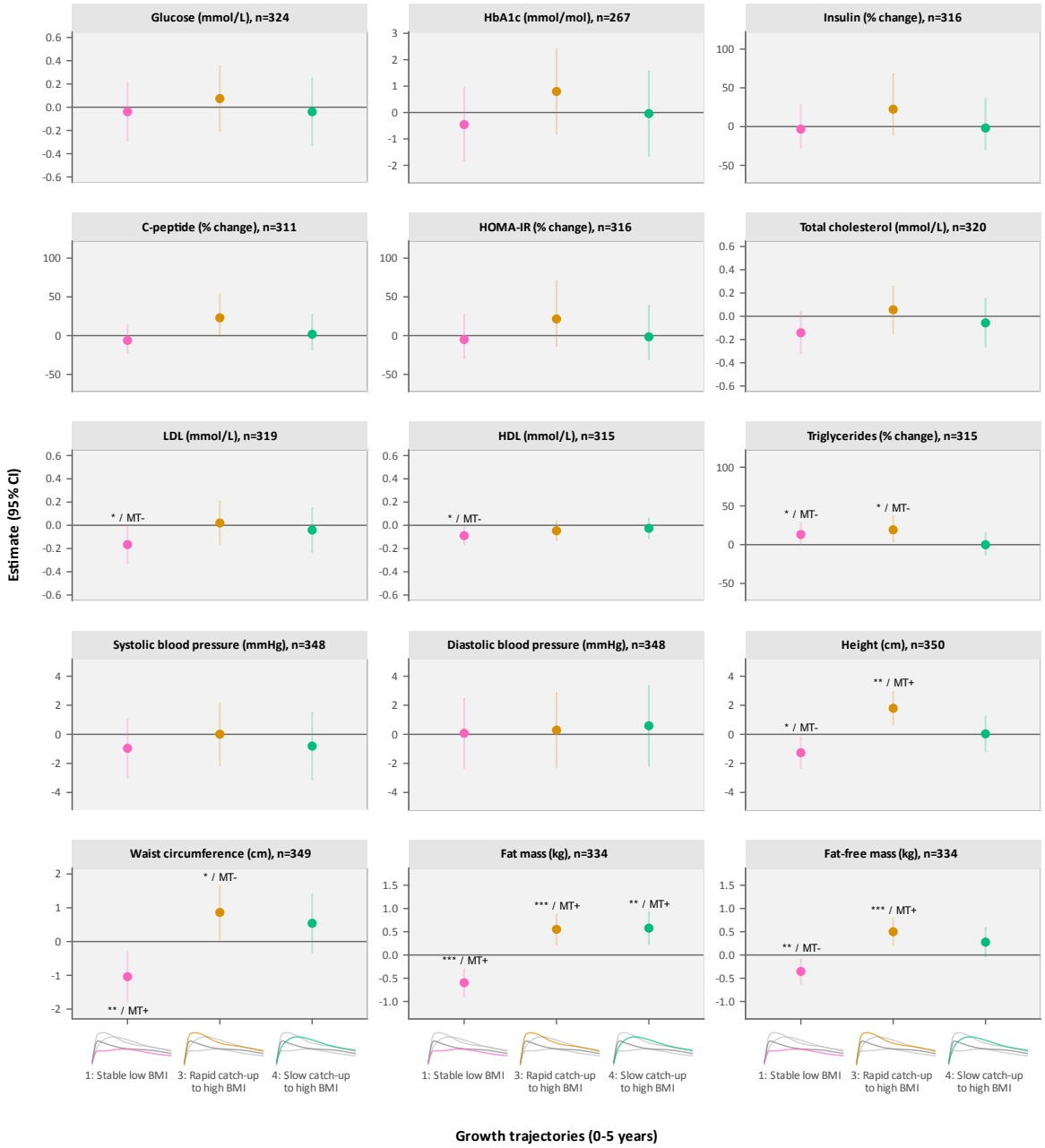
		1: Stable low BMI				3: Rapid catch-up to high BMI				4: Slow catch-up to high BMI			
	n	β	95% CI		p-value	β	95% CI		p-value	β	95% CI		p-value
Systolic blood pressure, mmHg	348												
Model 1		-1.8	-3.8	0.2	0.085	1.1	-1.0	3.3	0.307	-0.6	-3.0	1.7	0.588
Model 2		-1.7	-3.7	0.3	0.103	0.9	-1.2	3.0	0.389	-0.1	-2.4	2.2	0.942
Model 3		-1.6	-3.6	0.4	0.108	0.8	-1.4	2.9	0.487	-0.2	-2.5	2.1	0.887
Model 4		-1.0	-3.0	1.1	0.348	0.0	-2.1	2.2	0.993	-0.8	-3.1	1.5	0.493
Diastolic blood pressure, mmHg	348												
Model 1		-0.5	-2.9	1.9	0.664	1.1	-1.4	3.7	0.377	0.2	-2.5	3.0	0.877
Model 2		-0.4	-2.8	1.9	0.727	1.0	-1.5	3.5	0.446	1.1	-1.6	3.8	0.421
Model 3		-0.4	-2.7	2.0	0.743	0.8	-1.7	3.3	0.525	1.0	-1.7	3.8	0.451
Model 4		0.1	-2.3	2.5	0.950	0.3	-2.3	2.9	0.825	0.6	-2.2	3.3	0.674
Height, cm	350												
Model 1		-1.5	-2.7	-0.2	0.019	1.7	0.4	3.0	0.009	-0.5	-1.9	0.9	0.506
Model 2		-1.2	-2.2	-0.1	0.036	1.3	0.2	2.5	0.024	-0.2	-1.5	1.0	0.739
Model 3		-1.2	-2.2	-0.2	0.021	1.7	0.6	2.8	0.002	-0.0	-1.2	1.2	0.969
Model 4		-1.3	-2.3	-0.2	0.019	1.8	0.7	2.9	0.002	0.0	-1.2	1.2	0.959
Waist circumference, cm	349												
Model 1		-1.3	-2.1	-0.5	0.002	1.4	0.5	2.3	0.001	0.6	-0.3	1.5	0.199
Model 2		-1.3	-2.1	-0.5	0.002	1.3	0.5	2.2	0.003	0.6	-0.4	1.5	0.248
Model 3		-1.3	-2.1	-0.5	0.001	1.6	0.8	2.4	<.001	0.7	-0.2	1.6	0.140
Model 4		-1.0	-1.8	-0.3	0.006	0.9	0.1	1.7	0.035	0.5	-0.3	1.4	0.217
Fat mass, kg	334												
Model 1		-0.64	-0.98	-0.30	<.001	0.55	0.18	0.92	0.003	0.51	0.10	0.92	0.014
Model 2		-0.63	-0.97	-0.30	<.001	0.48	0.12	0.84	0.009	0.46	0.06	0.86	0.023
Model 3		-0.64	-0.96	-0.32	<.001	0.60	0.26	0.95	0.001	0.52	0.14	0.90	0.007
Model 4		-0.60	-0.89	-0.30	<.001	0.55	0.23	0.87	0.001	0.58	0.23	0.92	0.001
Fat-free mass, kg	334												
Model 1		-0.49	-0.88	-0.10	0.013	0.71	0.29	1.13	0.001	-0.04	-0.50	0.42	0.869
Model 2		-0.46	-0.83	-0.08	0.016	0.62	0.23	1.02	0.002	0.04	-0.40	0.48	0.848
Model 3		-0.47	-0.82	-0.12	0.009	0.77	0.39	1.15	<.001	0.12	-0.30	0.54	0.578
Model 4		-0.35	-0.62	-0.09	0.010	0.50	0.21	0.79	0.001	0.28	-0.04	0.59	0.083

[1] The coefficients (and 95% CIs) were derived from multiple linear regression models and represent the mean difference in concentrations of cardiometabolic markers and body composition indices between the reference trajectory (2: normal BMI) and the 3 BMI trajectory categories (1: stable low BMI; 3: rapid catch-up to high BMI; and 4: slow catch-up to high BMI). The 4 distinct BMI trajectories (exposure variable) were derived from a latent class trajectory modelling. The outcome variables of insulin, C-peptide, HOMA-IR, and triglycerides were log-transformed prior to analyses. The resulting effect estimates were back-transformed and are presented as the percentwise change. Model 1 was adjusted for child sex, birth order, and gestational age at birth. Model 2 was additionally adjusted for the child's exact age at the 5-year visit, maternal age at delivery, maternal postpartum height, maternal educational status, and family socioeconomic status (per the International Wealth Index). Model 3 was additionally adjusted for child birth weight. Model 4 was additionally adjusted for child BMI at the 5-year visit. In model 4, the analyses of FM and waist circumference were adjusted for FFM and height at 5 years instead of BMI, and the analysis of FFM was adjusted for FM and height at 5 years instead of BMI. [2] Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as insulin (μU/mL) × glucose (mmol/l) / 22.5.

Supplemental Figures

Supplemental Figure 1

Supplemental Figure 1. Accounting the regression results presented in the fully adjusted model (model 4) for multiple testing. The 5% alpha-level of significance was adjusted for multiple testing using the Benjamini–Hochberg approach where the number of tests was set to 45 (15 outcomes for 3 exposure groups). The significance stars on the left-hand side of the forward slash shows the significance-level before the adjustment and the text on the right-hand side shows if significance was achieved after adjusting for multiple testing. The designation "MT+" indicates that the significant association remained, and "MT-" indicates that the association were no longer significant after adjusting for multiple testing. * P<0.05, ** P<0.01, *** P<0.001.

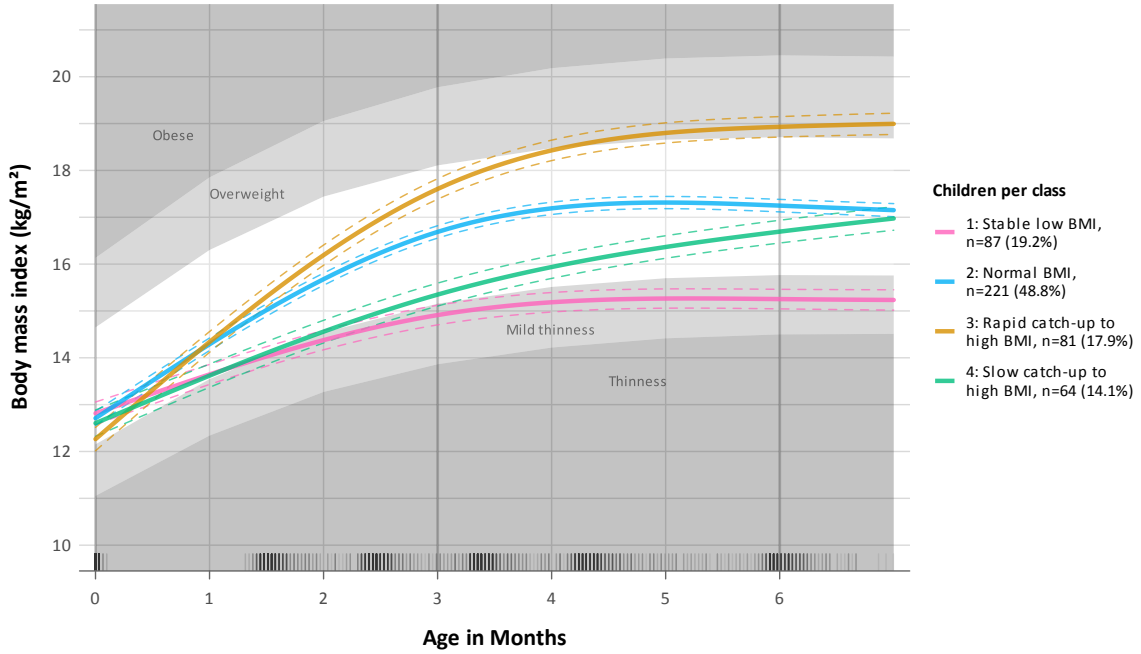


Supplemental Figure 2

Supplemental Figure 2. Sensitivity analyses of the associations of distinct body mass index (BMI) trajectories from 0-5 years with cardiometabolic markers and body composition at 5 years. The analyses are similar to those presented in Figure 4, with additional adjustments for breastfeeding status at 4 to 6 months post-partum in all models. The hollow circles show the estimates without adjustments for breastfeeding but based on the same subsample of children who have information on breastfeeding. Model 1 (the leftmost circle) was adjusted for child sex, birth order, gestational age at birth, and breastfeeding. Model 2 was additionally adjusted for the child's exact age at the 5-year visit, maternal age at delivery, maternal postpartum height, maternal educational status, family socioeconomic status (per the International Wealth Index). Model 3 was additionally adjusted for child birth weight. Model 4 (the rightmost circle) was additionally adjusted for child BMI at the 5-year visit. In model 4, the analyses of FM and waist circumference were adjusted for FFM and height at 5 years instead of BMI, and the analysis of FFM was adjusted for FM and height at 5 years instead of BMI. * P<0.05, ** P<0.01, *** P<0.001.

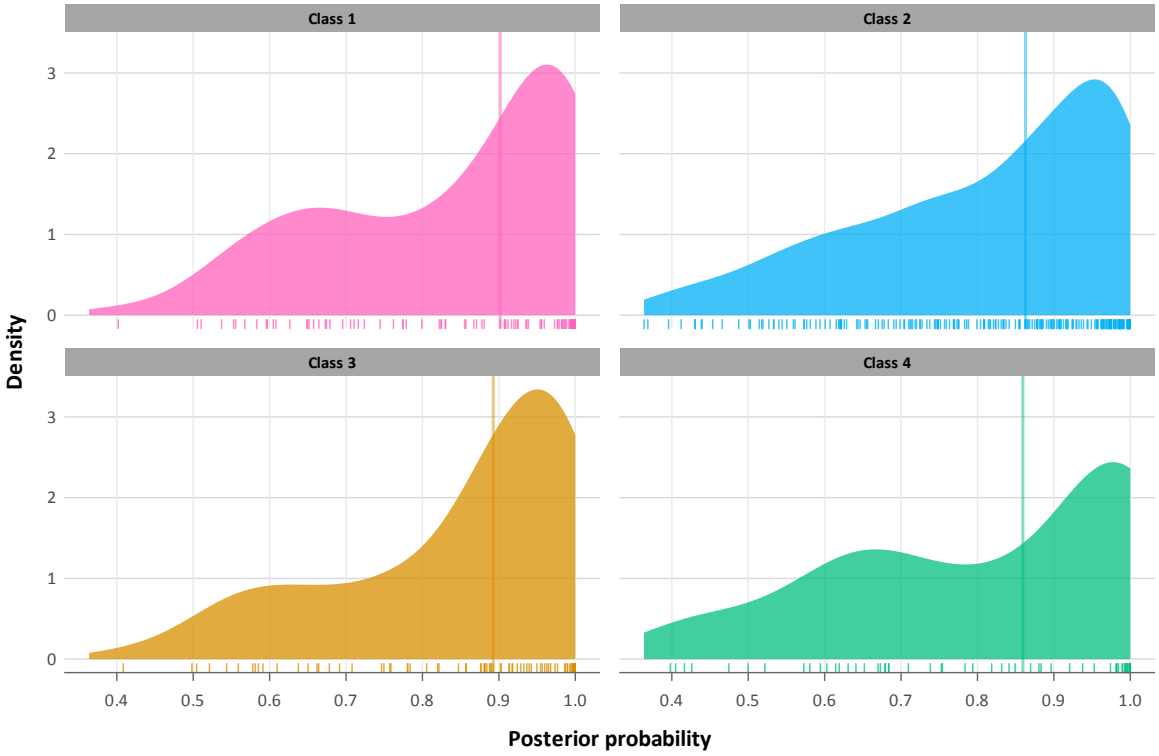
Supplemental Figure 3

Supplemental Figure 3. Distinct body mass index (BMI) trajectories from 0-6 months for children in the iABC birth cohort, derived from latent class trajectory modelling. The plot is based on the class assignments from the latent class trajectory modelling of BMI growth from 0-5 years. Solid lines display the class-specific estimated average BMI as a function of age. The dashed lines show the estimated 95% CIs. The shaded areas indicate the reference in SDs from the median BMI for age, according to the international growth standards developed by the WHO. A normal BMI (white) is defined as a BMI-for-age SD from −1 to 1, mild thinness as ≥−2 to <−1 SDs (light grey), thinness as <−2 SDs (grey), overweight as >1 to ≤2 SDs (light grey), and obese as >2 SDs (grey). The density of BMI observations is shown as a rug plot along the x-axis.



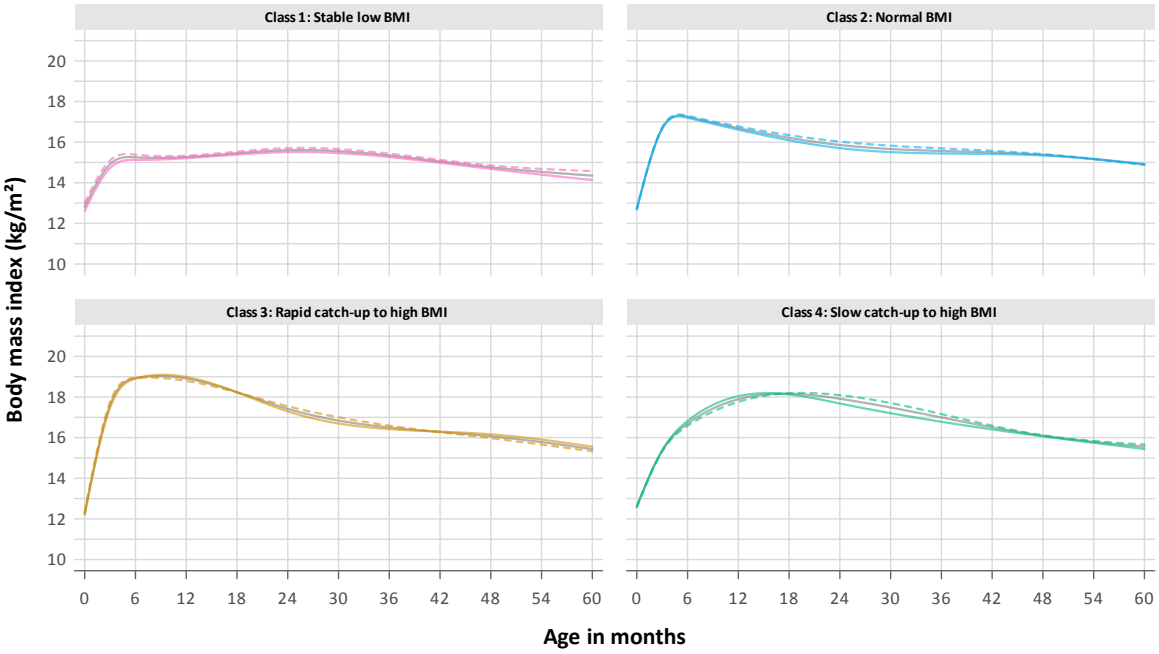
Supplemental Figure 4

Supplemental Figure 4. Distribution of posterior probabilities for assigned class membership. The dashed vertical lines show the median probabilities of assigned class membership.



Supplemental Figure 5

Supplemental Figure 5. Body mass index trajectories from 0-60 months for girls (solid lines), boys (dashed lines) and the whole study sample (solid grey lines) categorised using the class assignments from a latent class trajectory modelling.



Supplemental Methods

Detailed description of the latent class trajectory modelling

In the present study, latent class trajectory (LCT) modelling (also termed latent growth mixture modelling) was used to identify clusters (classes) of children who shared similar underlaying growth patterns of body mass index (BMI) from 0-5 years in the iABC birth cohort.

To account for the within-child correlations of repeated BMI measurements, we used a mixed-effect model as the underlying model structure. Thus, the estimated model parameters comprise both fixed and random effects. The fixed part includes the average intercept and slope (one for each identified class), expressing the average predicted BMI at birth and BMI growth trajectory over a specified time interval for each class, respectively. The random part includes the child-specific random intercepts and slopes expressing a child's deviations from the class average predicted BMI at birth and BMI growth trajectory over a specified time interval, respectively.

To best approximate the non-linear relationship of BMI as a function of age, we used a model specified with natural cubic splines with four internal knot point at 3, 6, 24 and 48 months and two boundary knot points at birth and 60 months. To identify the optimal number and placement of knot points, we ran several different models with knot points placed at the ages with a high density of BMI observation at the scheduled follow-up visits.

Subsequently, we fitted several LCT models with a different number of classes to identify the optimal number of distinct latent trajectories. We required a minimum of 5% of children in each BMI trajectory class, so that the classes would be clinically relevant and large enough to achieve a sufficient strata size for the subsequent linear regression analysis of the 5-year

outcomes. We selected the optimal model based on the Bayesian information criterion (smaller is better), log-likelihood, mean posterior probability of class membership (> 70% in each class), group size of the classes (> 5% of the study population) as well as the adequacy of the selected model to address the research question.[1-3]

The LCT model was specified using the "hlme" function in the R-package "lcmm" (version 1.7.8) in R (version 3.4.1).[4] The final model comprised 4 classes and was specified as follows:

```
hlme( fixed = BMI ~ Ns(age, knots = c(0, 3, 6, 24, 48, 60)),
      mixture = ~ Ns(age, knots = c(0, 3, 6, 24, 48, 60)),
      random = ~ age,
      subject = "id",
      ng = 4,
      data = Data)
```

, where the fixed term in the model specification included the response variable body mass index (BMI) and the covariate age in months specified using natural cubic splines. The function "Ns" in the R-package "Epi" was used to compute the natural cubic splines. The class-specific fixed effects were specified in the mixture term and a linear term of age defined the child ("id") specific random effects of the model (a random intercept is included by default).

References for Supplemental Methods

1. Lennon H, Kelly S, Sperrin M, et al. Framework to construct and interpret latent class trajectory modelling. *BMJ Open* 2018; **8**: e020683.

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4. Proust-Lima C, Philipps V, Liquet B. Estimation of Extended Mixed Models Using Latent Classes and Latent Processes: The R Package lcmm. *J Stat Softw* 2017; **78**: 1-56.