Online Supplement Appendix

Growth Trajectories and Asthma/Rhinitis in Children: a longitudinal study in Taiwan

Statistical Methods

Stage 1: Identification of distinct adiposity trajectories (age, 6–11 years)

Using the LGMM (latent generalized mixture model), we identified the number of subgroups of adiposity (mainly BMI z-scores) growth patterns from individual BMI z-score trajectories. The LGMM, an extension of the random effects of latent class growth model, refers to modeling with latent variables that used to identify heterogeneous subgroups with similar developmental trajectories (Figure E1). The random effects are allowed to have different distributions among individuals belonging to different trajectory classes. To check how closely the estimated average curve within each class matches the data, we can also use individual estimated conditional class probabilities to randomly assign individuals to classes. Missing data were appropriately managed in the LGMM with the assumptions of missing at random. This is in contrast to the typical longitudinal approach of multilevel modeling, which involves assuming that all trajectories of children can be modeled as a deviation from a common population slope. The following equations describe the model:

$$y_{it} = \eta_{0i} + \eta_1 age_t + \eta_2 age_t^2 + \eta_3 age_t^3 + \varepsilon_{it}$$

where y_{it} is the BMI z-score of children i at the measurement age$_t$ (years);

age_t is the age at year of measurement t = 6, 7, 8….11; and ε_{it} is the residual.

$$\eta_{0i} = \alpha_{0k} + \zeta_{0i}$$

η_{0i}: the latent variables of a random intercept; α_{0k}:means of an intercept for class k

$$\eta_1 = \alpha_{1k} + \zeta_1$$

η_1: the latent variables of a fixed linear slope; α_{1k}: means of a slope for class k

$$\eta_2 = \alpha_{2k} + \zeta_2$$

η_2: the latent variables of a fixed quadratic slope; α_{2k}: means of a quadratic slope for class k

$$\eta_3 = \alpha_{3k} + \zeta_3$$

η_3: the latent variables of a fixed cubic slope; α_{3k} means of a cubic slope for class k

Stage 2: Model adequacy assessment

For fitting the models with the same number of classes, the typical likelihood ratio chi-square test can be used. For calculating model performance indices for alternative models, we used the Bayesian Information Criterion (BIC) and Lo–Mendell–Rubin (LMR) test.[1] Lower BIC values, with significant results in the LMR test for a *k*-class model compared with a *k*−1-class model, suggested that the model fitted the data adequately when an additional latent class was included.

Stage 3: *Survival analysis*

We used the discrete time hazard model (DTHM), a survival analysis model that enables estimating hazard ratios (HRs) and 95% confidence intervals (CI) when the exact time to an event is unknown, but the period of event occurrence is known. The model was weighted by individual class probabilities, ω_{ik}, for each of the identified trajectory classes. The DTHM can be used to model the logit hazard according to the number of unit-coded time variables plus k−1 unit coded time trajectory class variables or other covariates that might predict hazard function differences. The DTHM is as follows:

$$\begin{aligned}\text{Logit h(tj)} = \sum_{k=1}^{4} \omega_{ik}([\alpha_1 D12 + \alpha_2 D15 + \alpha_3 D18] + \beta_1 C2 + \beta_2 C3 + \beta_3 C4 + \beta_4 Sex \\ + \beta_5 Age + \beta_6 Parental\ education\ level + \beta_7 Family\ income \\ + \beta_8 Household\ environmental\ tobacco\ smoke + \beta_9 BMI \\ + \beta_{10} Birth\ weight + \beta_{11} Gestation\ age + \beta_{12} Breastfeeding \\ + \beta_{13} Steroid\ use^*\end{aligned}$$

*Only used in Asthma

$\text{logit}\,\hat{h}(t_j) = \ln\left(\frac{\text{n events}_j}{\text{n at risk}_j}\right)$ α_1 to α_3: coefficients of the baseline hazard function.

D12, D15, D18: unit-coded time variables (age, 11-12, 13-15, and 16-18 years), and the periods for asthma and allergic rhinitis incidence.

Table E1. Estimates in the Latent Growth Mixture Model of four growth trajectory classes in Taiwan Children Health Study

	Class 1			Class 2			Class 3			Class 4		
Parameter	**Estimate**	**SE**	***p* value**	**Estimate**	**SE**	***p* value**	**Estimate**	**SE**	***p* value**	**Estimate**	**SE**	***p* value**
α_0	-0.114	0.030	0.000	-0.038	0.055	0.491	1.527	0.133	0.000	3.169	0.236	0.000
α_1	-0.110	0.022	0.000	-0.140	0.046	0.003	0.248	0.026	0.000	0.286	0.140	0.041
α_2	0.014	0.012	0.234	0.260	0.024	0.000	-0.050	0.015	0.001	-0.319	0.092	0.001
α_3	0.002	0.002	0.204	-0.036	0.003	0.000	0.001	0.002	0.671	0.041	0.012	0.001
$V(\zeta_{0i})$	0.828	0.035	0.000	0.828	0.035	0.000	0.828	0.035	0.000	0.828	0.035	0.000
$V(\zeta_{1i})$	0.000	0.000	999.000	0.000	0.000	999.000	0.000	0.000	999.000	0.000	0.000	999.000
$V(\zeta_2)$	0.000	0.000	999.000	0.000	0.000	999.000	0.000	0.000	999.000	0.000	0.000	999.000
$V(\zeta_3)$	0.000	0.000	999.000	0.000	0.000	999.000	0.000	0.000	999.000	0.000	0.000	999.000
$V(\varepsilon_{t1})$	0.320	0.034	0.000	0.320	0.034	0.000	0.320	0.034	0.000	0.320	0.034	0.000
$V(\varepsilon_{t2})$	0.133	0.009	0.000	0.133	0.009	0.000	0.133	0.009	0.000	0.133	0.009	0.000
$V(\varepsilon_{t3})$	0.147	0.009	0.000	0.147	0.009	0.000	0.147	0.009	0.000	0.147	0.009	0.000
$V(\varepsilon_{t4})$	0.159	0.012	0.000	0.159	0.012	0.000	0.159	0.012	0.000	0.159	0.012	0.000
$V(\varepsilon_{t5})$	0.164	0.016	0.000	0.164	0.016	0.000	0.164	0.016	0.000	0.164	0.016	0.000
$V(\varepsilon_{t6})$	0.233	0.014	0.000	0.233	0.014	0.000	0.233	0.014	0.000	0.233	0.014	0.000

SE, Standard Error of Estimate.

Table E2. Latent class estimates in the Latent Growth Mixture Model of four growth trajectory classes in Taiwan Children Health Study

Latent class estimates		
Parameter	**Estimate**	**SE**
α_{Class1}	2.458	0.284
α_{Class2}	1.859	0.334
α_{Class3}	1.963	0.246
α_{Class4}	0.000	Fixed

SE, Standard Error of Estimate.

Table E3. Model adequacy assessment for testing a *k−1*-class versus *k*-classes

		Lo-Mendell-Rubin test	
Number of classes	**BIC**	**Value**	**P value**
2	52327.180	52433.195	<0.001
3	51379.356	51518.492	<0.001
4	50934.950	51107.200	0.01
5	50549.633	50755.024	0.24

Table E4. Characteristics of participants in the Taiwan Children Health Study Cohort 1 at age 12, 15, 18, after separately excluding asthma (n=113) and allergic rhinitis (n=204) history children

Characteristics	Cohort 1 at 12 yrs	Cohort 1 at 15 yrs	Cohort 1 at 18 yrs
N	895	837	597
Male sex	453 (50.6%)	425 (50.8%)	307 (51.4%)
BMI, kg/m^2	20.5±4.3	21.2±4.3	21.1±4.2
Parental education, yrs			
Senior high school or below	600 (67.0%)	570 (68.1%)	400 (67%)
College or university	265 (29.6%)	242 (28.9%)	178 (29.8%)
Post-graduate school	30 (3.4%)	25 (3.0%)	19 (3.2%)
Family income, NTD*			
<600,000	543 (60.7%)	514 (61.4%)	354 (59.3%)
600,001-1,000,000	250 (27.9%)	232 (27.7%)	172 (28.8%)
>1,000,001	102 (11.4%)	91 (10.9%)	71 (11.9%)
Birthweight, gm	3193.5±445.6	3190.6±446.7	3201.3±450.1
Gestational age, wk	39.1±1.5	39.2±1.5	39.1±1.5
Breastfeeding	413 (46.2%)	376 (44.9%)	279 (46.7%)
Oral steroid use in recent 1 yr	3 (0.34%)	0 (0 %)	0 (0 %)
Household cigarette smoke	413 (46.2%)	455 (54.4%)	341 (57.1%)
Incident asthma, n (cases/1000 person-years)	18 (10.6)	12 (4.7)	14 (6.6)
Incident exercise-induced asthma, n (cases/1000 person-years)	22 (12.4)	138 (57.7)	77 (37.8)
Incident allergic rhinitis, n (cases/1000 person-years)	94 (62.1)	46 (20.4)	39 (21.4)
Trajectory classes			
Class 1	402 (44.9%)	375 (44.8%)	270 (45.2%)
Class 2	190 (21.2%)	182 (21.7%)	134 (22.5%)
Class 3	276 (30.8%)	256 (30.6%)	176 (29.5%)
Class 4	27 (3.0%)	24 (2.9%)	17 (2.9%)

All data are presented as means±SD or numbers (%).

The number of participants did not add up to the total number because of missing data.

*NTD: new Taiwan dollars.

Table E5. Odds ratios of asthma/rhinitis phenotypes according to the various growth trajectory classes at the age of 12 years

Trajectory classes	Active asthma*	Exercise-induced asthma*	Active allergic rhinitis†
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Cohort 1			
Class 1(ref)	1	1	1
Class 2	0.93 (0.35-2.51)	1.05 (0.46-2.37)	1.17 (0.81-1.70)
Class 3	1.39 (0.63-3.05)	1.05 (0.52-2.13)	1.45 (1.06-2.00)
Class 4	2.00 (0.42-9.55)	1.66 (0.36-7.67)	1.92 (0.89-4.14)
Cohort 2			
Class 1(ref)	1	1	1
Class 2	1.33 (0.82-2.16)	1.09 (0.73-1.63)	1.01 (0.81-1.26)
Class 3	1.63 (1.07-2.48)	1.57 (1.13-2.20)	1.09 (0.90-1.32)
Class 4	0.32 (0.04-2.41)	0.69 (0.21-2.25)	0.82 (0.47-1.43)

*Logistic regression models were adjusted for sex, age, parental education, family income, household environmental tobacco smoke, birthweight, gestational age, breastfeeding, and asthma oral steroid use.

†Logistic regression models were adjusted for sex, age, parental education, family income, household environmental tobacco smoke, birthweight, gestational age, and breastfeeding

Table E6. Association of FEV1/FVC ratios and fractional exhaled nitric oxide levels at the age of 12 years for the four growth trajectory classes

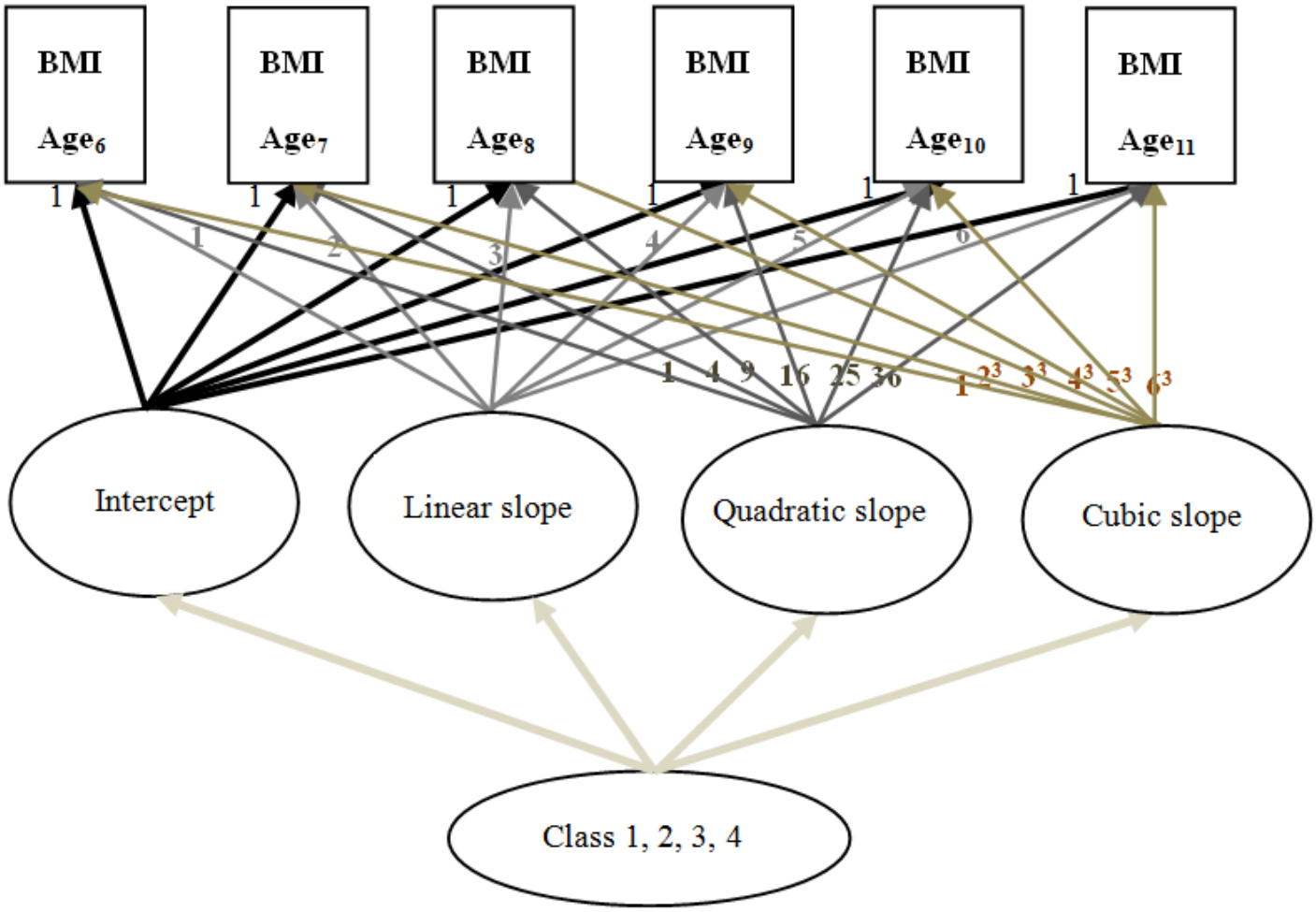
Variables	Class	Mean	95% CI	p values, compare with Class1
FEV1/FVC *	1	92.16	91.99-92.32	
	2	91.10	90.87-91.33	<0.001
	3	90.59	90.38-90.81	<0.001
	4	90.65	90.05-91.24	0.01
FeNO †	1	11.89	11.17 -12.92	
	2	10.80	9.32 -12.00	0.09
	3	10.41	9.16 -11.42	0.02
	4	14.44	10.18 -17.74	0.34

MANOVA were adjusted by sex, age, parental education, family income, household environmental tobacco smoke, birthweight, gestational age, breastfeeding, and asthma oral steroid use

* Cohort 1 and Cohort 2

† Cohort 2

Figure E1. Latent Growth Mixture Model for identifying growth trajectory classes.



Ovals represent latent variables, and rectangles represent indicators and other measured variables.

Figure E2. Age-specific and sex-specific BMI-z score trajectory classes across the ages 6–11 years, estimated using the Latent Growth Mixture Model (only Cohort 1).

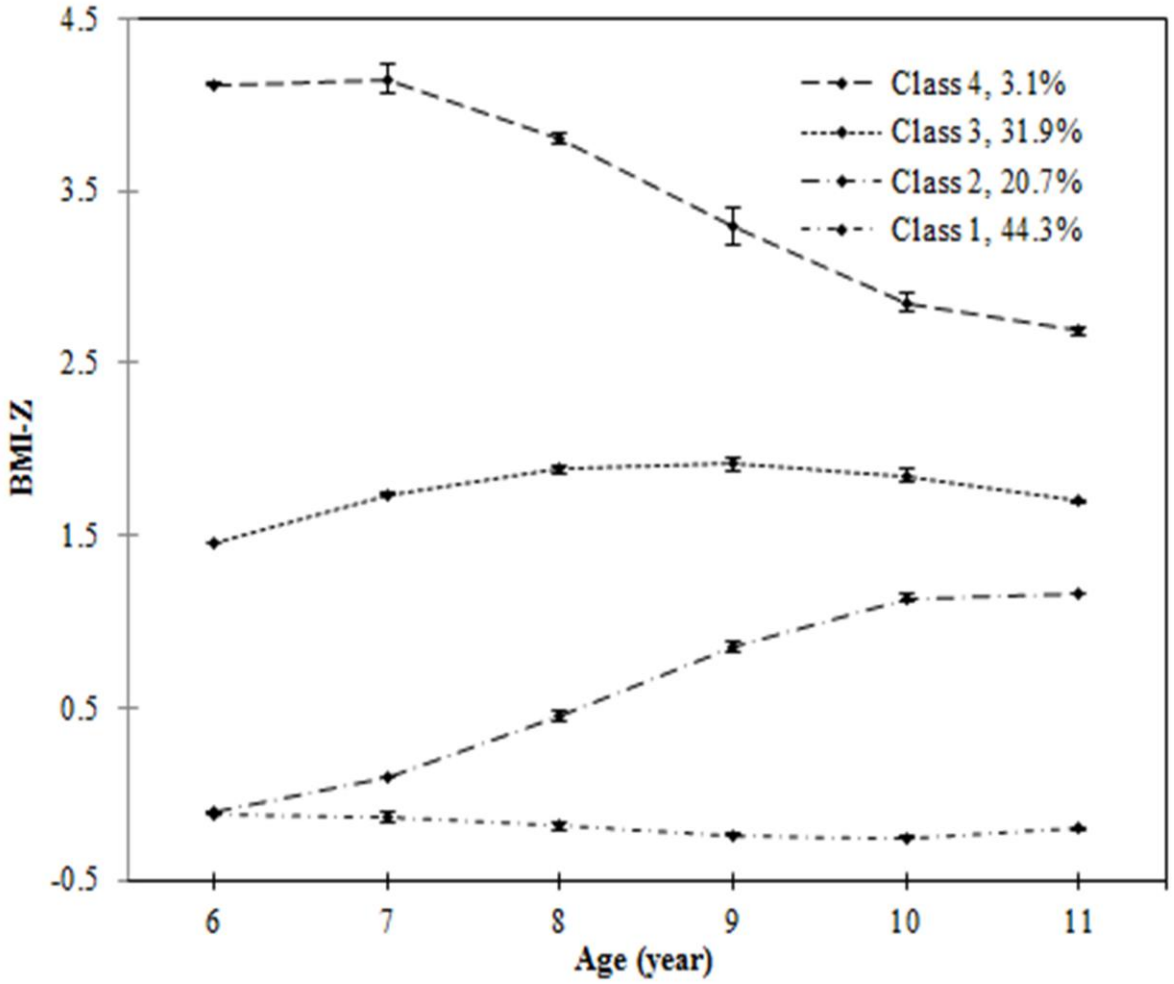


Figure E3. Age-specific and sex-specific BMI-z score trajectory classes across the ages 6–11 years, estimated using the Latent Growth Mixture Model (only Cohort 2).

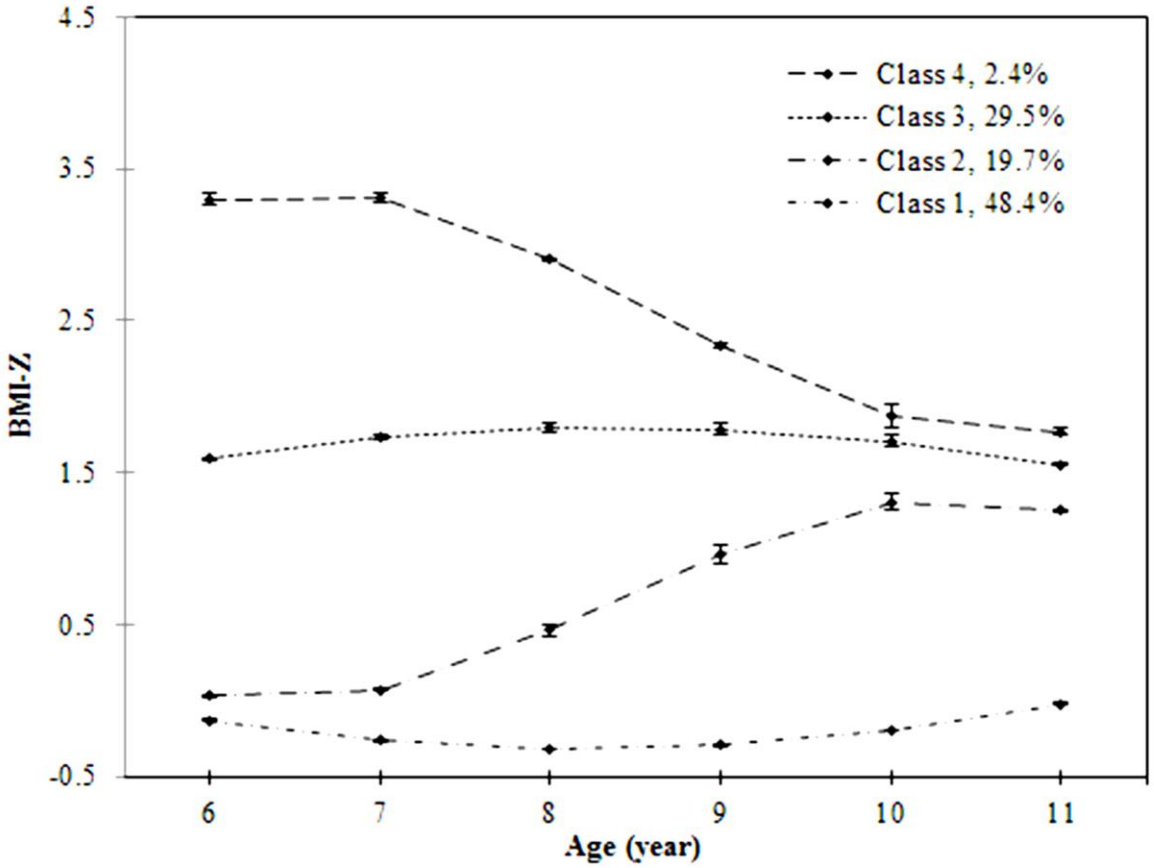


Figure E4. Age-specific BMI-z score trajectory classes across the ages 6–11 years, estimated using the Latent Growth Mixture Model (only boys).

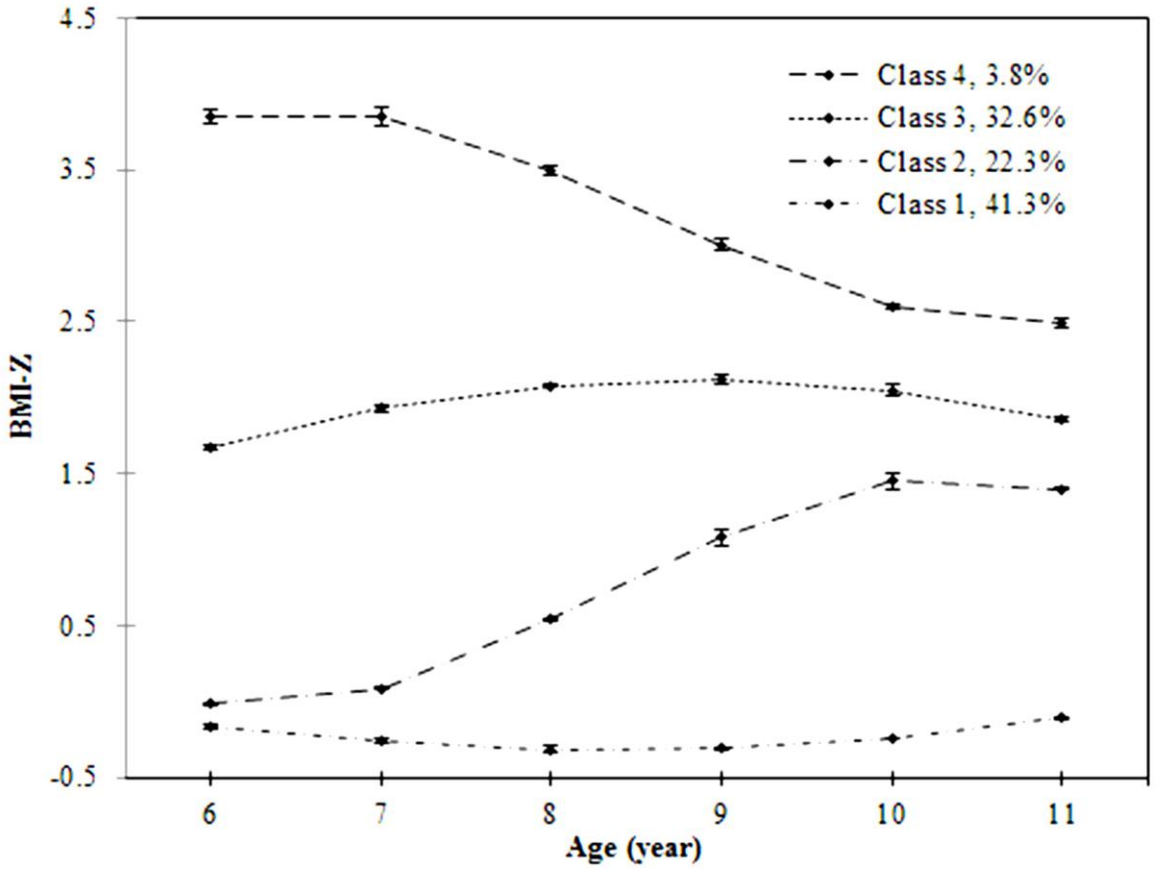
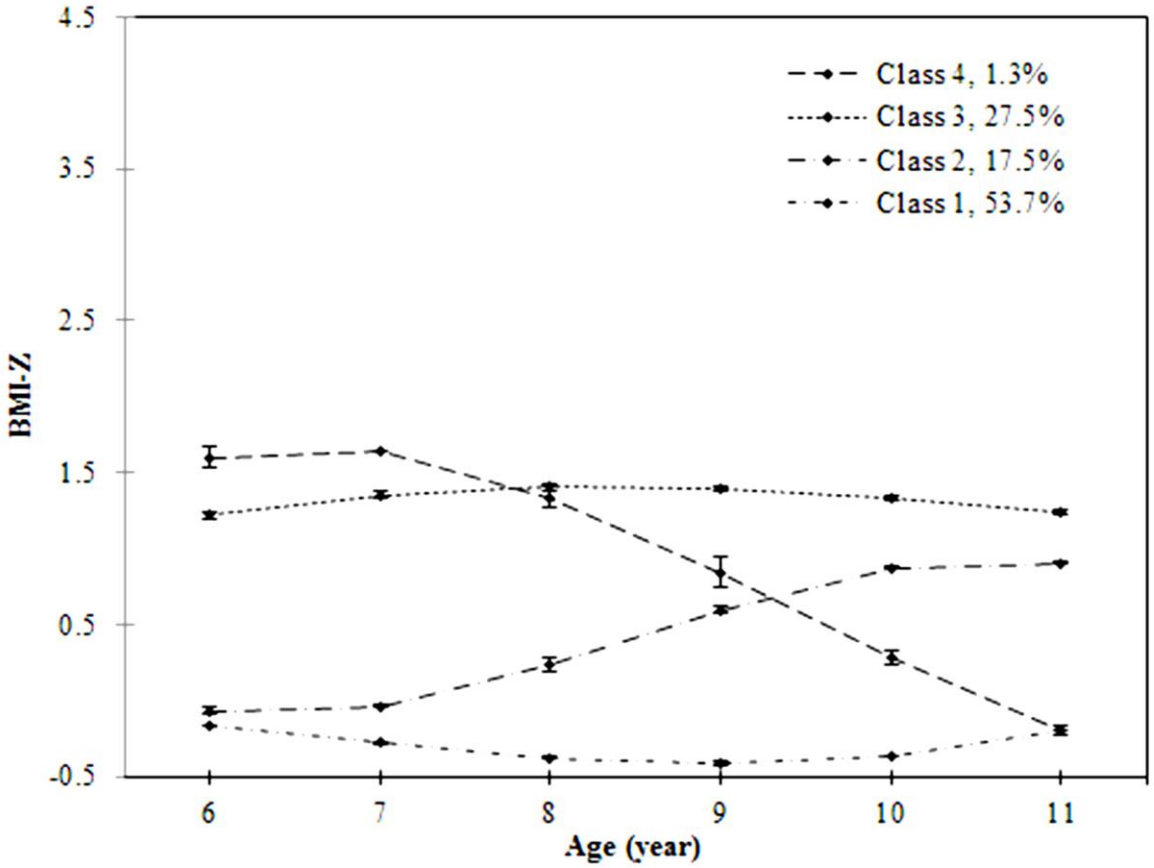


Figure E5. Age-specific BMI-z score trajectory classes across the ages 6–11 years, estimated using the Latent Growth Mixture Model (only girls).



References

1. Tein JY, Coxe S, Cham H. Statistical Power to Detect the Correct Number of Classes in Latent Profile Analysis. Structural equation modeling : a multidisciplinary journal 2013;20:640-57.