SUPPLEMENTAL MATERIAL

METHODS

REGISTRIES AND VARIABLES

The following section gives an overview of the registries used in our study. Data was linked across the different registries by the unique personal identification number (CPR number) that is assigned to each person residing in Denmark by the Danish Civil Registration System since 1968 (1).

The Danish National Patient Register (NPR) contains information on all somatic hospital discharges since 1977. Since 1995, the register also covers all outpatient specialty clinic contacts (1). From the NPR, we identified girls diagnosed with precocious puberty (International Classification of Diseases 10th revision (ICD-10): DE30.1), central precocious puberty (ICD-10: DE22.8A), and premature adrenarche (ICD-10: DE27.0B) (Table S3). To increase the validity of the diagnoses registered, we excluded girls that were not between 4-9 years old at the first date of diagnosis.

The Danish Medical Birth Register (DMBR) contains data on all births and pregnancies in Denmark since 1973 and covers around 99% of all deliveries in Denmark (2). In addition, maternal age, pre-pregnancy Body Mass Index (BMI), and smoking is reported. From the DMBR, we collected information on

- Birth weight (g)

  > 450 g & < 8000 g
- Birth length (cm)

  >20 cm & < 70 cm
- Gestational age (GA)

  Based on routine ultrasound scanning around 12 weeks of gestation
- Maternal pre-pregnancy BMI

  First pre-natal visit, selv-reported
- Maternal age at birth
- Maternal smoking

First pre-natal visit

Values of birth weight below 450 g or above 8000 g, as well as values of birth length below 20 cm or above 70 cm were computed as missing. Birth weight SDS was calculated based on Marsal (3) adjusted for sex (girl) and GA. Size at birth was categorized as either appropiate (AGA), small (SGA, below -2 SDS) or large (LGA, above +2 SDS) for gestational age. Maternal smoking status and BMI pre-pregnancy was registered at the first antenatal care visit and were self-reported. Maternal anthropometric values were computed as missing for height < 70 cm and > 240 cm, weight < 30 kg and > 250 kg, and for corresponding height, weight, and BMI beyond +/- 5 SDS.

The Danish National Child Health Register (CHR) was established in 2009 and consists of anthropometric measurements derived from preventive health examinations offered to all Danish children, either at home (several visits during the first year of life), at the general practitioner (ages 5 weeks, 5 months, annually 1- 5 years), or at school (ages 6-15 years) (4,5). Reporting to the CHR became mandatory as of December 2011. The validity of the registry is confirmed from 2012 onward, and the coverage during the years 2012-2018 was between 80-94% (4). From the CHR, we retrieved data on height (cm) and weight (kg) for calculating BMI (kg/m^2) from after birth and until 10 years of age. Age-adjusted Z-scores based on the WHO growth standards for girls were calculated using the R-package "zscorer" (version 0.3.1) (6).

Values of birth weight, birth length, weight, height, and BMI were all computed as missing if values were ≤ 0, if values were +/- 7 SDS, or if values were considered implausible based on age or corresponding height/weight (n=2).

The Population Education Register (PER) contains information on Danish individuals' highest completed education (7). In 2008, the coverage was 96% for individuals aged 15-69 years. From the PER, we collected information on the mother's highest completed education at the year of birth. Educational level was classified based on the International Standard Classification of Education (ISCED).

Data on household income at the year of birth was obtained from the Income Statistics Register (ISR) and reported as family income deciles, adjusted for the number of individuals living in the household. The ISR covers economically

active individuals who has submitted a tax return to the Danish Tax Administration and contains more than 160 variables on income, pension, socioeconomic status, and more (8).

DETAILED DESCRIPTION, LATENT CLASS TRAJECTORY MODELLING

We used the *hlme()* function from the package *lcmm* (version 2.1.0) in R (The R Foundation for Statistical Computing (version 4.4.1)) to determine the final LCT models. Initially, we ran a one class-model to determine the initial values for the optimisation algorithm.

m1 <- *hlme(fixed = BMI ~ Ns(age, knots = c(0.0, 0.5, 1.0, 3.0, 6.5, 10.0)),*

random = ~ age,

subject = "id",

ng = 1,

data = Data

Subsequently, the gridsearch function within the *lcmm* package was employed to execute the *hlme* function a total of 30 times, utilizing varying initial values as specified by the "rep" argument, and conducting ten iterations as indicated by the "maxiter" argument (see below). This methodology was implemented to mitigate the risk of the model converging at a local optimum and was applied to models specified by 2-5 classes.

A mixed effect model was used as the underlying model structure to account for individual correlations of repeated BMI measurements, including both fixed and random effects of the estimated model parameters. The fixed effects expressed the average BMI at birth (intercept) and BMI trajectory (slopes within specified time intervals) for each class. The random effects comprised the individual intercepts and slopes, thereby reflecting each individual's deviation from the average predicted intercepts and slopes of the specific class.

For the precocious puberty population, the best fitting model was obtained with a 3-class model specified with natural cubic splines with internal knot points at 0.5, 1, 3, and 6.5 years, and boundary knots at birth and 10 years. The final model was specified as outlined below:

m3 <- g*ridsearch(rep = 30, maxiter = 10, minit = m1)*

hlme(fixed = BMI ~ Ns(age, knots = c(0.0, 0.5, 1.0, 3.0, 6.5, 10.0)),

mixture = ~ Ns(age, knots = c(0.0, 0.5, 1.0, 3.0, 6.5, 10.0)),

random = ~ age,

subject = "id",

ng = 3,

data = Data)

where the *fixed* term comprised the response variable BMI and the covariate age in years. The model was specified with natural cubic splines through the utilization of the *Ns()* function within the R package *Epi* (version 2.59) to best approximate the non-linear relationship of BMI as a function of age. The *mixture* term encapsulated the class-specific fixed effects. A linear term representing age defined the individual ("*id*")-specific *random* effects within the model. *ng* refers to number of classes in the model.

Results from the model assessments are presented below in Tables S1 & S2.

The overall mean estimated BMI trajectories for the two study populations are shown in Figure S1. Plots of the models with 2, 4 and 5 classes are presented below (Figures S2 (precocious puberty) and S3 (premature adrenarche)).

REFERENCES

1. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National patient registry: A review of content, data quality, and research potential. *Clin Epidemiol*. 2015;**7**:449-490. doi:10.2147/CLEP.S91125

2. Bliddal M, Broe A, Pottegård A, Olsen J, Langhoff-Roos J. The Danish Medical Birth Register. *Eur J Epidemiol*. 2018;**33**(1):27-36.

3. *Length/Height-for-Age, Weight-for-Age, Weight-for-Length, Weight-for-Height and Body Mass Index-for-Age Methods and Development*.

4. Andersen MP, et al. The Danish National Child Health Register. *Clin Epidemiol*. 2023;**15**:1087-1094. doi:10.2147/CLEP.S423587

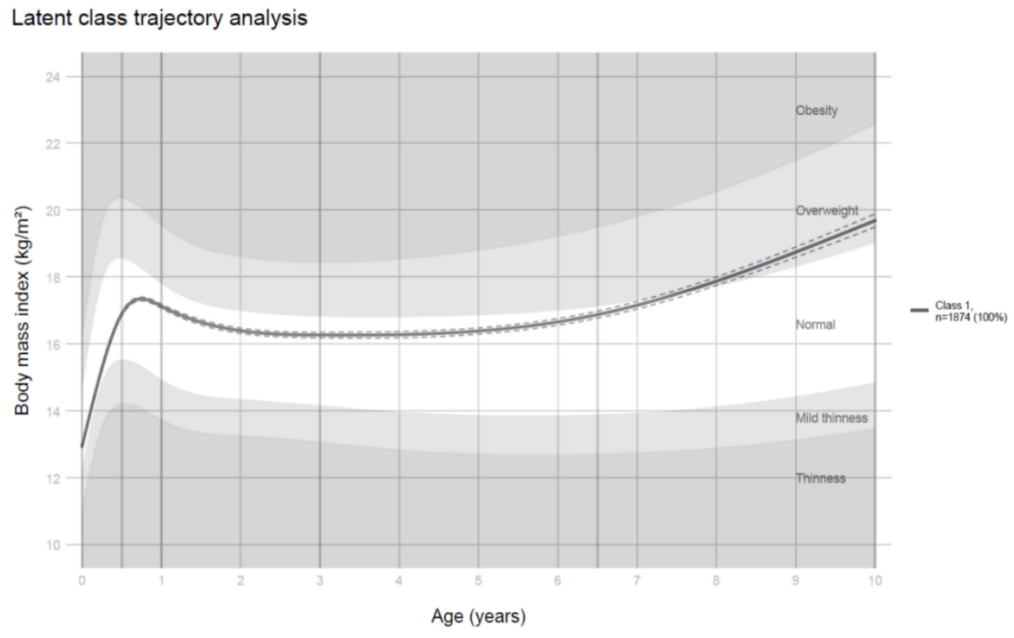
5. Bjerager MO, et al. *Monitoring Growth in 0–5 Year Old Children: Guidance for Health Visitors and General Practitioners.*; 2015.

6. Myatt M, Guevarra E. Package 'zscorer.' 2025;0.3.1.

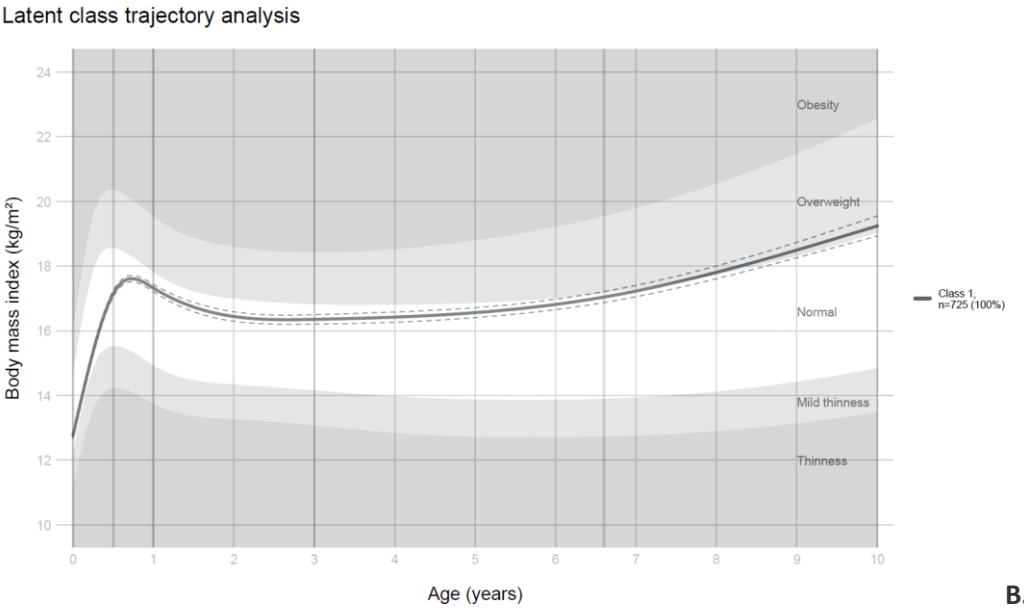
7. Jensen VM, Rasmussen AW. Danish education registers. *Scand J Public Health*. 2011;**39**(7):91-94. doi:10.1177/1403494810394715

8. Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. *Scand J Public Health*. 2011;**39**(7):103-105. doi:10.1177/1403494811405098

FIGURES AND TABLES



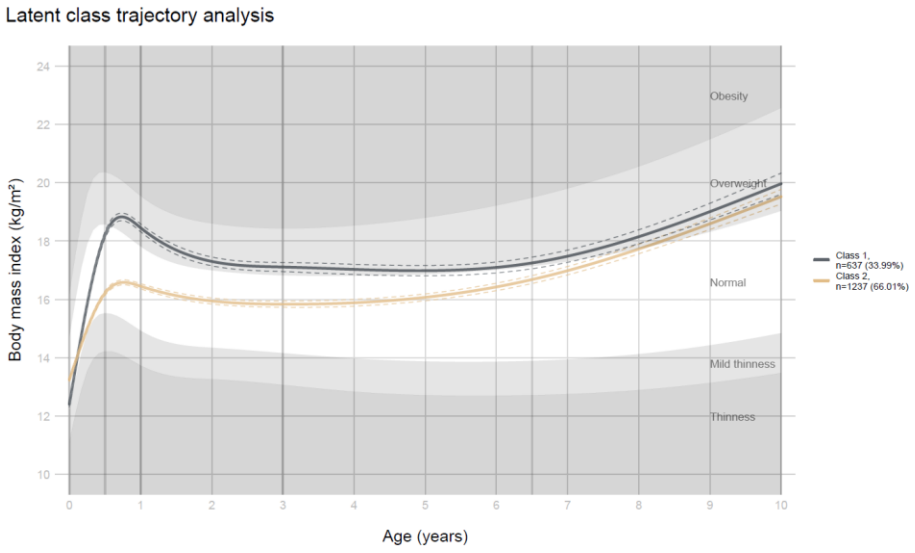
A.



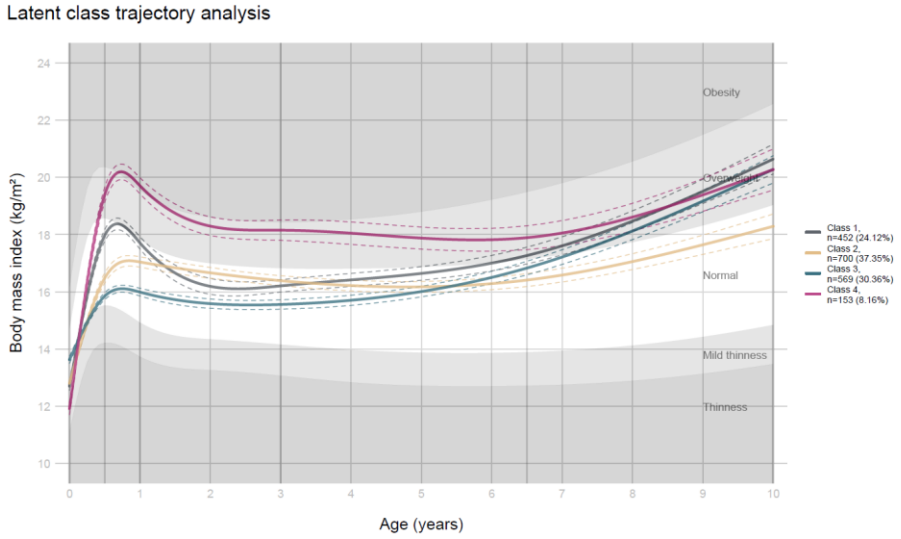
B. **B.**

Figure S1. Body mass index (BMI) trajectories from birth to 10 years of age were identified for the entire population of girls diagnosed with A: Precocious puberty (n = 1874) and B: Premature adrenarche (n = 725) using latent class trajectory (LCT) modelling. Solid curves represent the estimated mean BMI for each trajectory group across age, while dashed curves denote the corresponding 95% confidence intervals. Background shading indicates BMI-for-age standard deviation categories relative to the WHO international growth reference median. Normal BMI (white)

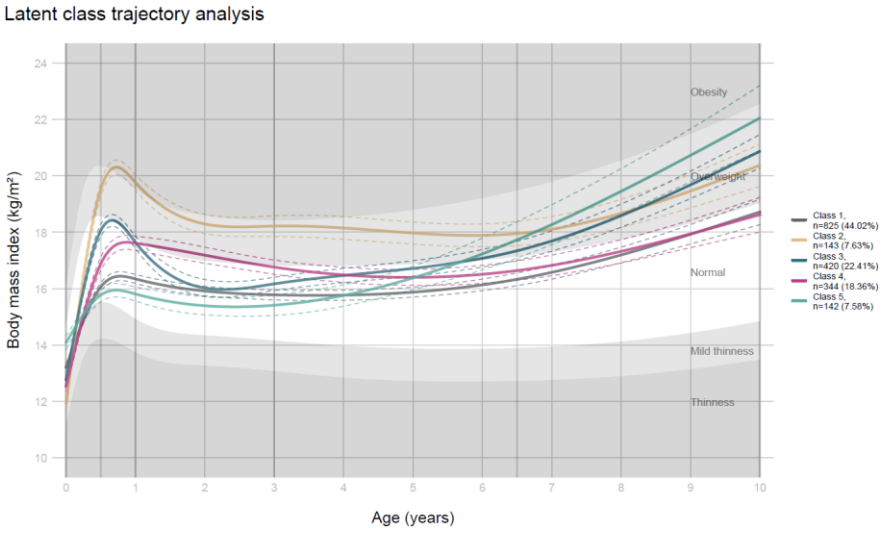
was defined as −1 to +1 SD, mild thinness (light gray) as ≥ −2 to < −1 SD, thinness (gray) as < −2 SD, overweight (light gray) as > +1 to ≤ +2 SD, and obesity (gray) as > +2 SD.



A.

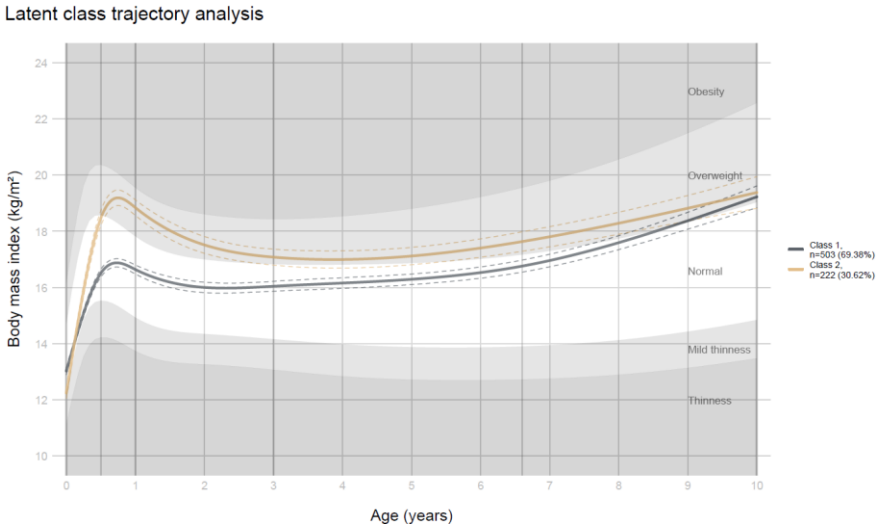


B.

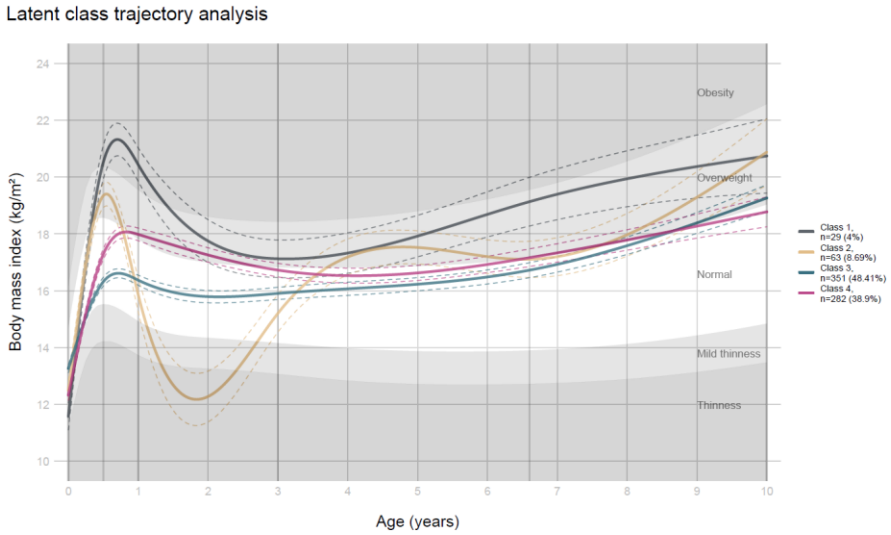


C.

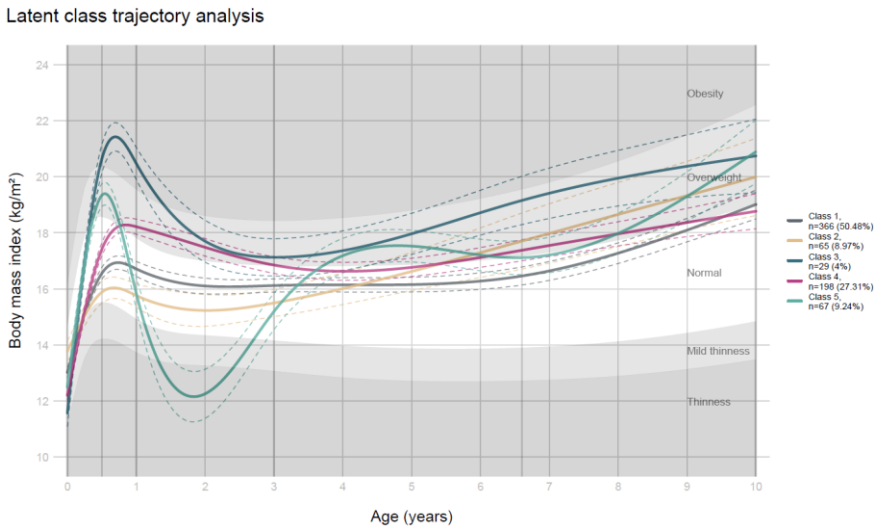
Figure S2. Precocious puberty. LCT modelling of BMI from birth to ten years with A: Two classes identified; B: Four classes identified; C: Five classes identified. Solid curves represent the estimated mean BMI for each trajectory group across age, while dashed curves denote the corresponding 95% confidence intervals. Background shading indicates BMI-for-age standard deviation categories relative to the WHO international growth reference median. Normal BMI (white) was defined as −1 to +1 SD, mild thinness (light gray) as ≥ −2 to < −1 SD, thinness (gray) as < −2 SD, overweight (light gray) as > +1 to ≤ +2 SD, and obesity (gray) as > +2 SD.



A.

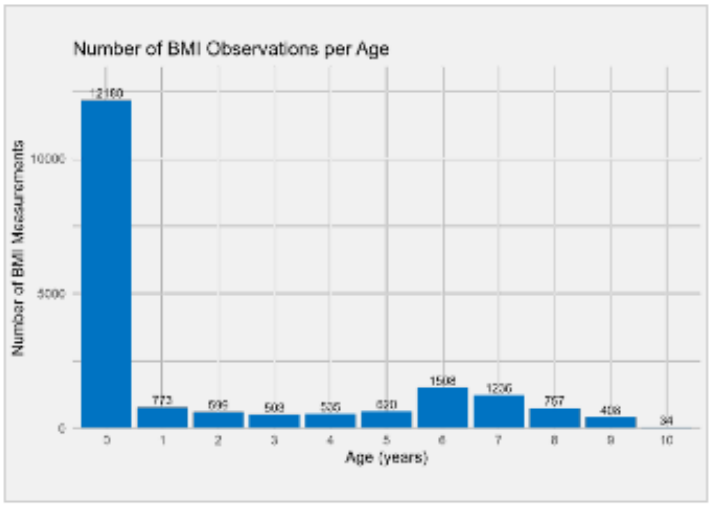


B.

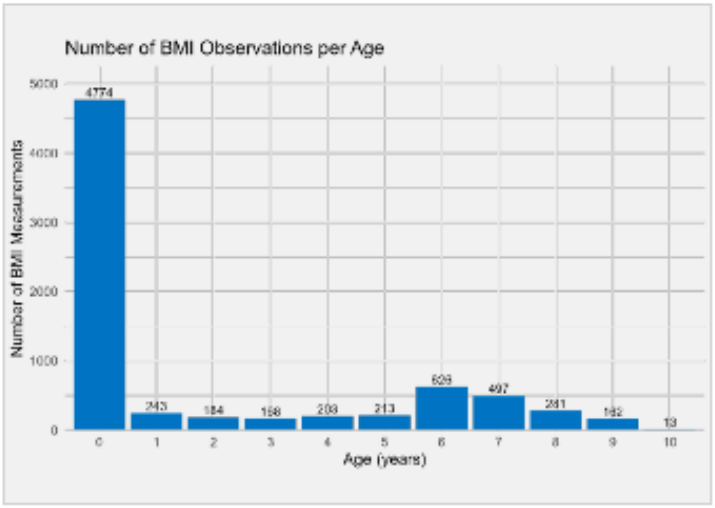


C.

Figure S3. Premature adrenarche. LCT modelling of BMI from birth to ten years with A: Two classes identified; B: Four classes identified; C: Five classes identified. Solid curves represent the estimated mean BMI for each trajectory group across age, while dashed curves denote the corresponding 95% confidence intervals. Background shading indicates BMI-for-age standard deviation categories relative to the WHO international growth reference median. Normal BMI (white) was defined as −1 to +1 SD, mild thinness (light gray) as ≥ −2 to < −1 SD, thinness (gray) as < −2 SD, overweight (light gray) as > +1 to ≤ +2 SD, and obesity (gray) as > +2 SD.



A.



B.

Figure S4. Number of BMI measurements according to age. A: Girls with precocious puberty. B: Girls with premature adrenarche.

Number of classes	Class	Proportion per class (%)	Mean posterior probability assignment (%) Class I	II	III	IV	V	BIC	AIC	Relative entropy
1	1	100	**100**					64809	64753	1.00
2	1	34.0	**0.97**					62513	62419	0.72
	2	66.0		**0.99**						
3	1	52.6	**0.91**					61910	61777	0.72
	2	9.2		**0.97**						
	3	38.1			**0.93**					
4	1	24.1	**0.77**					61731	61559	0.62
	2	37.3		**0.72**						
	3	30.3			**0.87**					
	4	8.2				**0.96**				
5	1	44.0	**0.80**					61660	61450	0.62
	2	7.6		**0.95**						
	3	22.4			**0.71**					
	4	18.4				**0.64**				
	5	7.6					**0.84**			

Table S1. Model adequacy assessment of different number of classes in the latent class trajectory modelling of girls diagnosed with precocious puberty from birth to age 10 years (n = 1874).

Number of classes	Class	Porportion per class (%)	Mean posterior probability assignment (%) Class I	II	III	IV	V	BIC	AIC	Relative entropy
1	1	100	**100**					25217	25171	1
2	1	69.4	**99**					24469	24391	0.72
	2	30.6		**96**						
3	1	7.2	**90**					24224	24114	0.73
	2	46.1		**91**						
	3	46.8			**94**					
4	1	4	**100**					24104	23962	0.75
	2	8.7		**86**						
	3	48.4			**95**					
	4	38.9				**87**				
5	1	50.5	**85**					24069	23894	0.71
	2	9		**80**						
	3	4			**99**					
	4	27.3				**84**				
	5	9.2					**87**			

Table S2. Model adequacy assessment of different number of classes in the latent class trajectory modelling of girls diagnosed with premature adrenarche from birth to age 10 years (n = 725).

Diagnosis	ICD-10 code	Clinical Criteria
Central Precocious Puberty Precocious Puberty	DE22.8A DE30.1	Development of secondary sexual characteristics before eight years of age (in a girl) due to activation of the hypothalamic-pituitary-gonadal (HPG)-axis.
Premature Adrenarche	DE27.0B	Development of axillary and pubic hair growth, acne, and/or odor before eight years of age (in a girl) due to the production of adrenal androgens.

Table S3. Diagnoses retrieved from the National Patient Register (NPR). International Classification of Diseases 10th revision (ICD-10).