Online only supplementary material

Article title: Developmental trajectories of body mass index from infancy to 18 years of age: prenatal determinants and health consequences

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Table S1. Summary and comparison of published studies investigating the developmental trajectories of body mass index

Study	Age span	Sample size	Study design	Phenotypic variables	Analytical methods	Trajectories
Mustillo et al., 2003[23]	9 – 16 yrs	991	Longitudinal study	Obese and non-obese categories	Semiparametric mixture model	- Never obese - Adolescent obese - Obese - Childhood obese
Li et al., 2007[24]	2 – 12 yrs	1739	Cohort study	Overweight and non-overweight categories	Growth mixture model	- Normal - Early-onset - Late-onset
Ventura et al., 2009[25]	5 – 15 yrs	182 (girls only)	Longitudinal study	Relative value of BMI (percentile = pct)	Growth mixture model	- Upward pct crossing - Delayed downward pct crossing - 50^{th} pct tracking - 60^{th} pct tracking
Nonnemaker et al., 2009[26]	12 – 23 yrs	6784	Accelerated longitudinal design	Absolute value of BMI	Growth mixture model	- High risk of overweight - Moderate-to-high risk of overweight - Low-to-moderate risk of overweight - Low-risk of overweight
Pryor et al., 2011[28]	0.5 – 8 yrs	1957	Prospective cohort study	Absolute value of BMI	Semiparametric mixture model	- Low-stable BMI - Moderate BMI - High-rising BMI
Haga et al., 2012[29]	1.5 – 12 yrs	1518	Longitudinal study	BMI z-scores	Semiparametric mixture model	- Stable thin - Stable average - Stable higher average - Progressive average - Progressive overweight - Progressive obesity
Magee et al., 2013[27]	4 – 11 yrs	4601	Longitudinal study	Absolute value of BMI	Growth mixture model	- Healthy weight - High risk overweight - Early onset overweight - Late onset overweight
Huang et al., 2013[30]	6 – 18 yrs	5156	Cohort study	Obese and non-obese categories	Semiparametric mixture model	- Non-obese - Increasing - Decreasing - Chronically obese

BMI: Body mass index

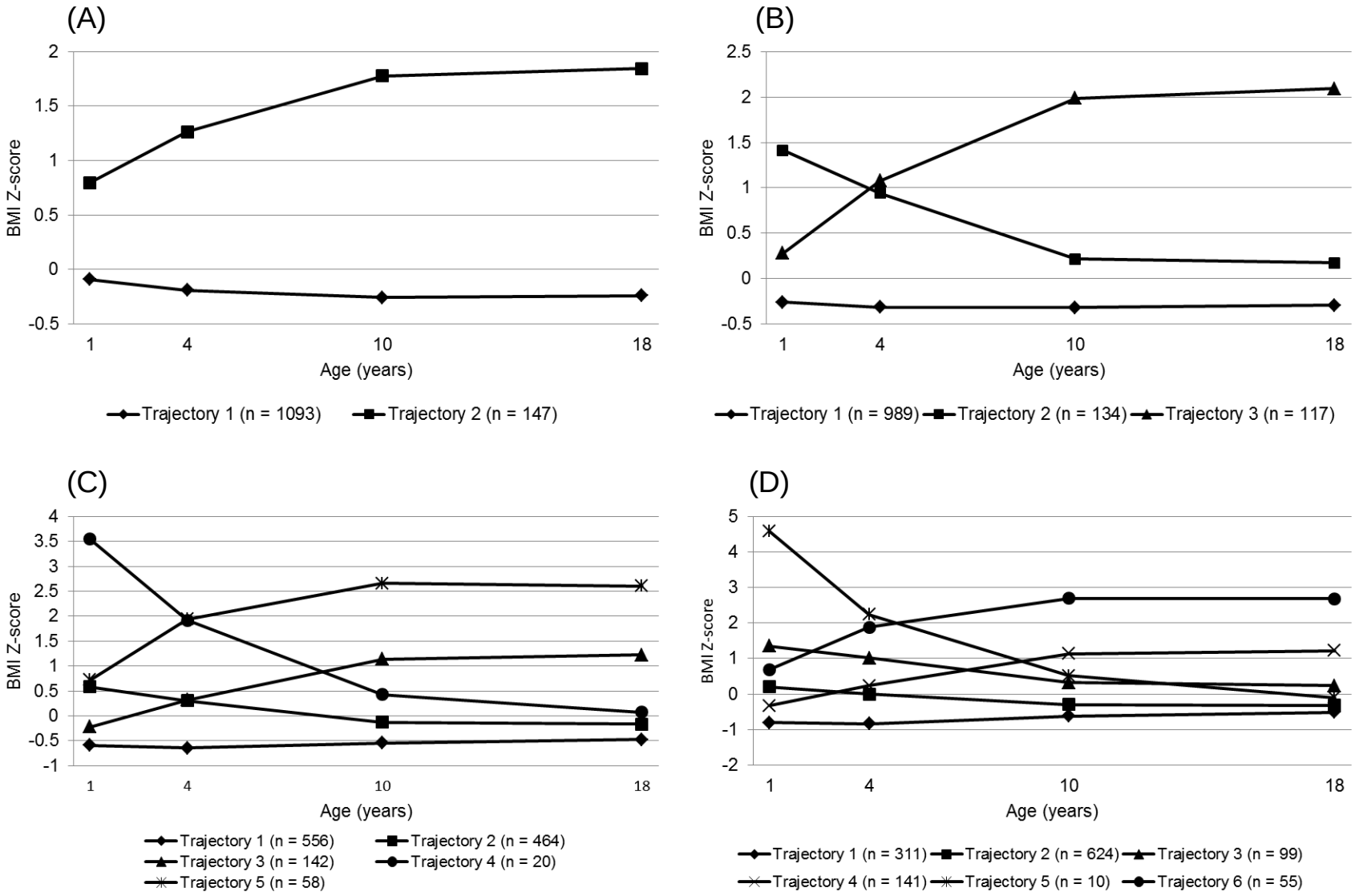

Figure S1. BMI z-score trajectories from 1 to 18 years of age. (A) Shows a model with two trajectories. (B) Shows a model with three trajectories. (C) Shows a model with five trajectories. (D) Shows a model with six trajectories.

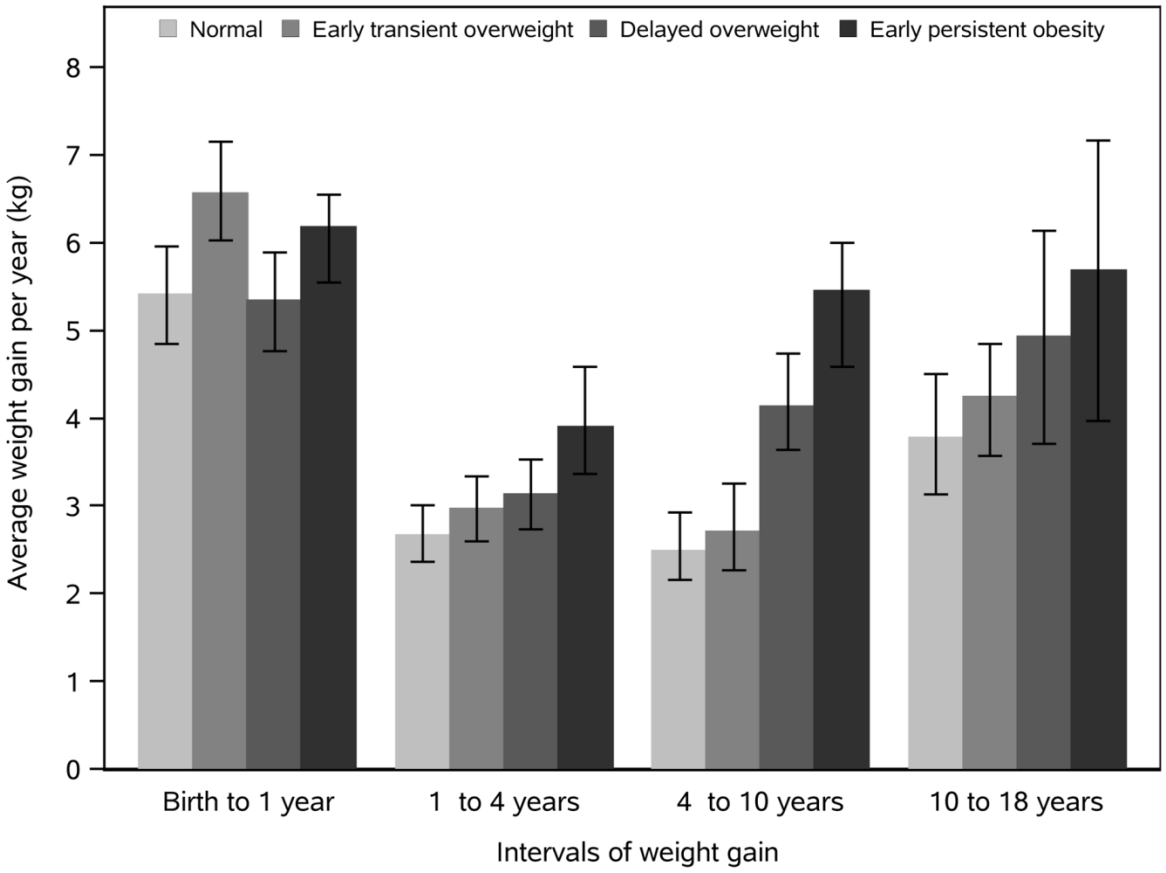

Figure S2. Weight gain across body mass index z-score trajectories during different developmental periods. Average weight gain (kg) per year was calculated for each trajectory during the different developmental periods. Error bars represent first (25^{th} percentile) and third (75^{th} percentile) quartiles.

Online Results I:

Average weight gain per year was estimated for each of the four trajectories across different developmental time-windows (figure S2). The early persistent obesity trajectory experienced higher weight gain than the normal trajectory across all developmental periods. For instance, average weight gain from birth to age 1 was 6.14 kg among participants in the early persistent obesity trajectory; whereas those in the normal trajectory gained on average 5.40 kg during the same period. The early transient overweight trajectory demonstrated substantially higher weight gain than the normal trajectory between birth and 1 year. The delayed overweight trajectory started gaining on average more weight than the normal trajectory between age 1 and 4 years.

Sensitivity analysis I: Excluding participants who self-reported their anthropometric measurements at ages 10 (n = 2) and 18 (n = 91) years. Analytical sample size = 1147 participants.

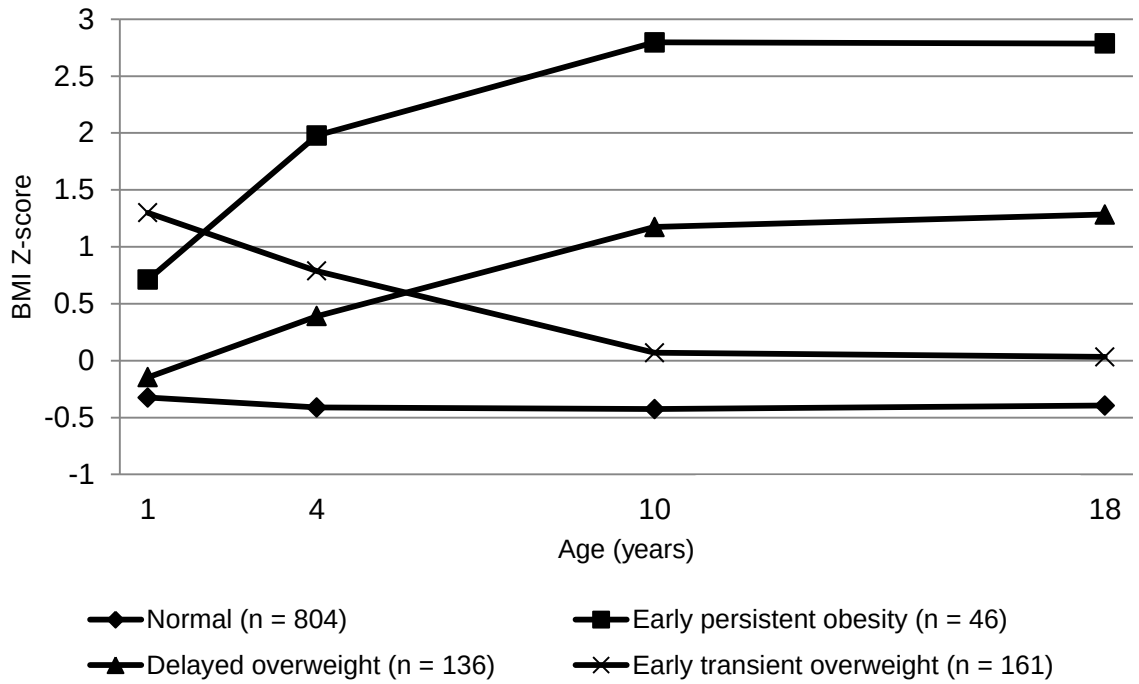

Figure S3. BMI z-score trajectories based on participants who had their anthropometric measurements directly measured at the research center (n = 1147). [Sensitivity analysis I]

Sensitivity analysis I: Continued

Table S2. Associations of maternal smoking during pregnancy and maternal early-pregnancy overweight (BMI ≥ 25.0) with offspring BMI z-score trajectories [Sensitivity analysis I]

	Sex-adjusted model			
	Maternal smoking during pregnancy		**Maternal early-pregnancy BMI (kg/m^2)**	
BMI z-score trajectories	**No (n = 694)**	**Yes (n = 193)**	**< 25.0 (n = 591)**	**≥ 25.0 (n = 296)**
Normal (Reference), No. (%)	497 (71.6)	115 (59.6)	435 (73.6)	177 (59.8)
Early persistent obesity, No. (%)	26 (3.8)	11 (5.7)	16 (2.7)	21 (7.1)
RR (95% CI)	1.00	1.79 (1.01 to 3.48)	1.00	2.94 (1.57 to 5.51)
p Value		0.043		< 0.001
Delayed overweight, No. (%)	76 (11.0)	33 (17.1)	50 (8.5)	59 (19.9)
RR (95% CI)	1.00	1.69 (1.18 to 2.41)	1.00	2.39 (1.70 to 3.36)
p Value		0.004		< 0.001
Early transient overweight, No. (%)	95 (13.7)	34 (17.6)	90 (15.2)	39 (13.2)
RR (95% CI)	1.00	1.38 (0.97 to 1.95)	1.00	1.07 (0.76 to 1.50)
p Value		0.065		0.694
	Adjusted model*			
	Maternal smoking during pregnancy		**Maternal early-pregnancy BMI (kg/m^2)**	
BMI z-score trajectories	**No (n = 615)**	**Yes (n = 151)**	**< 25.0 (n = 509)**	**≥ 25.0 (n = 257)**
Normal (Reference), No. (%)	432 (70.2)	86 (57.0)	370 (72.7)	148 (57.6)
Early persistent obesity, No. (%)	19 (3.1)	9 (6.0)	12 (2.4)	16 (6.2)
RR (95% CI)	1.00	2.17 (1.01 to 4.71)	1.00	3.22 (1.56 to 6.68)
p Value		0.046		0.002
Delayed overweight, No. (%)	76 (12.4)	28 (18.5)	47 (9.2)	57 (22.2)
RR (95% CI)	1.00	1.79 (1.22 to 2.62)	1.00	2.52 (1.78 to 3.57)
p Value		0.003		< 0.001
Early transient overweight, No. (%)	88 (14.3)	28 (18.5)	80 (15.7)	36 (14.0)
RR (95% CI)	1.00	1.40 (0.95 to 2.06)	1.00	1.08 (0.77 to 1.54)
p Value		0.093		0.630

BMI: Body mass index; RR: Risk ratio; CI: Confidence interval; No.: Number;
* Adjusted for sex, birth weight, gestational age at birth, maternal age at delivery, duration of breastfeeding, maternal education, and socioeconomic status.

Sensitivity analysis I: Continued

Table S3. BMI z-score trajectories as predictors of asthma, FEV_1/FVC ratio, and blood pressure at 18 years of age [Sensitivity analysis I]

	BMI z-score trajectories			
Health outcomes at 18 years	**Normal**	**Early persistent obesity**	**Delayed overweight**	**Early transient overweight**
Asthma, % (n/total)	16.2 (109/672)	36.1 (13/36)	26.6 (33/124)	16.0 (20/125)
RR (95% CI)[*]	1.00 (Reference)	2.08 (1.29 to 3.35)	1.58 (1.12 to 2.23)	0.96 (0.62 to 1.49)
p Value		0.003	0.009	0.859
FEV1/FVC (%), mean (SE)	87.7 (0.5)	84.5 (1.4)	85.9 (0.8)	87.4 (0.8)
Mean difference (95% CI)[£]	0.0 (Reference)	-3.2 (-6.0 to -0.4)	-1.8 (-3.3 to -0.3)	-0.2 (-1.8 to 1.4)
p Value		0.028	0.018	0.844
Systolic BP (mm Hg), mean (SE)	106.7 (0.7)	117.9 (2.1)	112.6 (1.3)	107.6 (1.3)
Mean difference (95% CI)[£]	0.0 (Reference)	11.2 (7.1 to 15.3)	6.0 (3.6 to 8.4)	0.9 (-1.6 to 3.4)
p Value		< 0.001	< 0.001	0.479
Diastolic BP (mm Hg), mean (SE)	63.7 (0.5)	75.7 (1.6)	69.3 (0.9)	66.5 (1.0)
Mean difference (95% CI)[£]	0.0 (Reference)	12.0 (8.9 to 15.1)	5.6 (3.8 to 7.4)	2.8 (0.9 to 4.6)
p Value		< 0.001	< 0.001	0.004

BMI: Body mass index; BP: Blood pressure; RR: risk ratio; CI: confidence interval; SE: Standard error;
[*] Adjusted for sex, smoking status at age 18 years, duration of breastfeeding, and socioeconomic status
[£] Adjusted for sex, height at age 18 years, smoking status at age 18 years, duration of breastfeeding, and socioeconomic status

Sensitivity analysis II: Assessing the association between BMI at age 18 years with health outcomes at age 18 years.

Table S4. BMI at age 18 years as predictor of asthma, FEV_1/FVC ratio, and blood pressure at 18 years of age [Sensitivity analysis II]

	BMI at age 18 years		
Health outcomes at 18 years	**Normal (BMI < 25.0)**	**Overweight (25.0 ≤ BMI < 30.0)**	**Obese (BMI ≥ 30.0)**
Asthma, % (n/total)	16.8 (106/633)	19.6 (26/133)	29.4 (20/68)
RR (95% CI)[*]	1.00 (Reference)	1.15 (0.78 to 1.69)	1.56 (1.06 to 2.56)
p Value		0.491	0.021
FEV1/FVC (%), mean (SE)	87.9 (0.5)	86.3 (0.7)	85.6 (0.9)
Mean difference (95% CI)[£]	0.0 (Reference)	-1.6 (-3.3 to -0.4)	-2.3 (-4.5 to -0.7)
p Value		0.013	0.009
Systolic BP (mm Hg), mean (SE)	106.0 (0.7)	112.4 (1.1)	117.6 (1.5)
Mean difference (95% CI)[£]	0.0 (Reference)	6.4 (4.3 to 8.7)	11.6 (8.8 to 14.5)
p Value		< 0.001	< 0.001
Diastolic BP (mm Hg), mean (SE)	63.7 (0.5)	67.7 (0.9)	74.1 (1.2)
Mean difference (95% CI)[£]	0.0 (Reference)	4.0 (2.3 to 5.6)	10.4 (8.2 to 12.6)
p Value		< 0.001	< 0.001

BMI: Body mass index; BP: Blood pressure; RR: risk ratio; CI: confidence interval; SE: Standard error;
[*] Adjusted for sex, smoking status at age 18 years, duration of breastfeeding, and socioeconomic status
[£] Adjusted for sex, height at age 18 years, smoking status at age 18 years, duration of breastfeeding, and socioeconomic status

Sensitivity analysis III: Assessing the association of BMI trajectories and BMI at age 18 years with health outcomes at age 18 years. Both, BMI trajectories and BMI at age 18 years, in addition to other potential confounders, were included in the regression models.

Table S5. Association of BMI trajectories and BMI at age 18 years with health outcomes at age 18 years [Sensitivity analysis III]

	BMI z-score trajectories				**BMI at age 18 years**		
Health outcomes at 18 years	**Normal**	**Early persistent obesity**	**Delayed overweight**	**Early transient overweight**	**Normal (BMI < 25.0)**	**Overweight (25.0 ≤ BMI < 30.0)**	**Obese (BMI ≥ 30.0)**
Asthma, % (n/total)	16.2 (97/599)	37.9 (11/29)	24.8 (28/113)	17.2 (16/93)	16.8 (106/633)	19.6 (26/133)	29.4 (20/68)
RR (95% CI)[*]	1.00 (Reference)	2.63 (1.08 to 6.35)	1.68 (1.02 to 2.92)	0.96 (0.62 to 1.49)	1.00 (Reference)	0.88 (0.54 to 1.46)	0.85 (0.40 to 1.81)
p Value		0.032	0.046	0.859		0.628	0.675
FEV1/FVC (%), mean (SE)	86.8 (0.8)	85.4 (1.6)	86.3 (0.7)	86.6 (1.0)	87.4 (0.8)	85.5 (0.8)	85.5 (1.1)
Mean difference (95% CI)[£]	0.0 (Reference)	-1.4 (-5.2 to 2.4)	-0.5 (-3.6 to 1.6)	-0.2 (-1.8 to 1.5)	1.00 (Reference)	-1.2 (-3.3 to 0.07)	-1.7 (-4.7 to 1.0)
p Value		0.469	0.648	0.834		0.102	0.216
Systolic BP (mm Hg), mean (SE)	112.2 (1.2)	113.4 (2.4)	111.2 (1.3)	112.1 (1.5)	106.0 (1.2)	112.9 (1.3)	117.8 (1.7)
Mean difference (95% CI)[£]	0.0 (Reference)	1.2 (-4.4 to 6.8)	-1.0 (-4.3 to 2.2)	-0.1 (-2.6 to 2.4)	1.00 (Reference)	6.9 (4.3 to 9.5)	11.8 (7.4 to 16.2)
p Value		0.668	0.536	0.955		< 0.001	< 0.001
Diastolic BP (mm Hg), mean (SE)	67.0 (0.9)	72.8 (1.8)	68.5 (0.9)	69.4 (1.2)	65.8 (0.9)	69.0 (1.0)	73.4 (1.3)
Mean difference (95% CI)[£]	0.0 (Reference)	5.8 (1.6 to 10.0)	1.4 (-1.0 to 3.9)	2.3 (0.4 to 4.3)	1.00 (Reference)	3.1 (1.2 to 5.1)	7.6 (4.3 to 11.0)
p Value		0.007	0.253	0.016		0.002	<0.001

BMI: Body mass index; BP: Blood pressure; RR: risk ratio; CI: confidence interval; SE: Standard error;
[*] Adjusted for sex, smoking status at age 18 years, duration of breastfeeding, and socioeconomic status
[£] Adjusted for sex, height at age 18 years, smoking status at age 18 years, duration of breastfeeding, and socioeconomic status

Online Results II:

Table S4 presents results of the associations between BMI at age 18 years with health outcomes. Obesity (BMI ≥ 30.0) at 18 years is associated with a 1.56-fold increased risk of asthma, 2.3% decrease in FEV_1/FVC ratio, and 11.6 mm Hg and 10.4 mm Hg increase in systolic and diastolic blood pressure, respectively. Hence, indicating that concurrent obesity is associated with health outcomes. Although comparing the effect sizes of the 'early persistent obesity' trajectory to effect sizes of obesity (BMI ≥ 30) at age 18 years shows that early persistent obesity is associated with higher effect sizes on asthma (RR = 2.15 vs. RR = 1.56) and FEV_1/FVC ratio (mean difference = -3.2 vs. mean difference = -2.3), these results should be interpreted with caution since the categorizes defining obesity are different. For instance, individuals in the 'early persistent obesity' trajectory have a mean BMI of 34.9 kg/m^2 at age 18 years; whereas, obesity at age 18 years was define as BMI ≥ 30 kg/m^2.

In regard to blood pressure at 18 years, both obesity at 18 years and the 'early persistent obesity' trajectory yielded similar effect sizes. For instance, the 'early persistent obesity' trajectory and obesity at 18 years were associated with increased systolic blood pressure by 11.3 mm Hg and 11.6 mm Hg, respectively. The increase in diastolic blood pressure was slightly higher when comparing the 'early persistent obesity' trajectory (12.0 mm Hg) and obesity at 18 years (10.4 mm Hg). Taken together, blood pressure is not noticeably influenced by the early-onset persistent obesity.

In further analyses, we ran regression models that included both BMI trajectories and BMI at age 18 years to determine which variable accounts for the observed associations with health outcomes (table S5). When asthma is the outcome variable, the 'early persistent obesity' and 'delayed overweight' trajectories remained statistically significant with no reduction in their effect sizes (RR = 2.63, P-value = 0.032 and RR = 1.68, P-value = 0.046, respectively) while controlling for BMI at 18 years. In contrast, obesity at age 18 years, while controlling for BMI trajectories, did not increase the risk of asthma (RR = 0.85, P-value = 0.675). Hence, further demonstrating that the duration of overweight-obesity is important factor in the development of asthma (even after controlling for the effect of current BMI). When FEV_1/FVC ratio is the outcome variable, neither BMI trajectories nor BMI at age 18 years, while simultaneously controlling for their effects, showed statistically significant associations. Hence, indicating that, in addition to the duration and intensity of adiposity, the current BMI is also a contributor to the association between early persistent obesity and lung function parameters. In regard to blood pressure, BMI at age 18 years, while controlling for the effect of BMI trajectories, statistically significantly associated with blood pressure. Whereas, BMI trajectories, while controlling for BMI at age 18 years, lost statistical significance and also their effect sizes were reduced. Thus, indicating that current adiposity is sufficient for explaining blood pressure.

A possible concern for the models that included both BMI trajectories and BMI at age 18 years is the presence of collinearity since BMI trajectories were derived by the use of BMI at age 18 years. For the purpose of assuring model adequacy, we performed collinearity diagnostics for the models that included both BMI trajectories and BMI at age 18 years (table S5). We used 'Tolerance', defined as 1/variance inflation factor (VIF), to check for possible collinearity (rule of thumb: tolerance value less than 0.1 is an indicator of possible collinearity in the model). Results of these diagnostic tests showed that none of the variables in our models had a 'tolerance' value close to 0.1 (the smallest 'tolerance' value we observed was 0.43 for BMI at age 18 years while modeling FEV_1/FVC ratio; data not shown).

Table S6. BMI z-score trajectories as predictors of asthma at age 10 years

	Asthma at age 10 years	
BMI z-score trajectories	**RR (95% CI)***	**p Value**
Normal	1.00	
Early persistent obesity	1.67 (0.87 to 3.21)	0.126
Delayed overweight	1.41 (0.94 to 2.13)	0.098
Early transient overweight	1.15 (0.75 to 1.76)	0.507

* Adjusted for sex, duration of breastfeeding, and socioeconomic status

Online Methods I: Potential confounders

For the association between maternal prenatal characteristics (i.e., maternal early-pregnancy overweight and gestational smoking) and offspring BMI trajectories, we tested two models: the first model was only adjusted for sex, whereas, in the second model we adjusted for potential confounders including sex, birth weight, gestational age at birth, maternal age at delivery, duration of breastfeeding, maternal education, and socioeconomic status. The association between BMI trajectories and asthma at 18 years was adjusted for sex, smoking status at age 18 years, duration of breastfeeding, and socioeconomic status. The previous covariates plus height at age 18 years were adjusted for when testing the associations between BMI trajectories with FEV_1/FVC ratio and systolic and diastolic blood pressure. The adjustment for the aforementioned covariates was based on prior knowledge in published literature (and the availability of the variables in our study), which indicated the possibility of the respective covariates in attenuating the association being tested.

The following covariates were included in the regression models as categorical variables: sex (male, female), birth weight (< 2.5 kg, 2.5 – 4.0 kg, > 4.0 kg), socioeconomic status (low, middle, upper), smoking status at 18 years (yes, no); whereas, gestational age at birth (weeks), maternal age at delivery (years), duration of breastfeeding (weeks), maternal education (years of formal education completed by the mother), height (cm) at age 18 years were considered as continuous variables.

The socioeconomic status was characterized by clusters composed of the following information: 1) the British socioeconomic classes (1–6) [1], derived from parental occupation reported at birth; 2) the number of children in the index child's bedroom (collected at 4 yrs of age); and 3) family income at 10 yrs of age. This composite variable captures the family social class across the first 10 years of life [2]. Family social status cluster was categorized as low, middle, and upper class.

References

1. The Office for National Statistics. The National Statistics Socioeconomic Classification: Origins, Development and Use. Basingstoke, Palgrave Macmillan, 2005.

2. Ogbuanu IU, Karmaus W, Arshad SH, et al. Effect of breastfeeding duration on lung function at age 10 years: a prospective birth cohort study. Thorax 2009; 64: 62–66.