Association of height growth in puberty with lung function: a longitudinal study

Online Data Supplement

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METHODS

Participants

ALSPAC initially recruited 14,541 pregnant women resident in Avon, UK with expected dates of delivery between April 1, 1991 and December 31, 1992. This initial number of pregnancies, known as core sample, included the mothers enrolled in the ALSPAC study and had either returned at least one questionnaire or attended a 'Children in Focus' research clinic by 19th July 1999. These initial pregnancies had a total of 14,676 fetuses, resulting in 14,062 live births and 13,988 children who were alive at age 1 year. When the oldest children were approximately seven years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, there are extra data available when considering variables collected from the age of seven years onwards. The number of new pregnancies, not in the core sample, known as phases II and III enrolments, is 706 (452 and 254 recruited during Phases II and III respectively), resulting in an additional 713 children being enrolled. The phases of enrolment are described in more detail in the

cohort profile paper (1). Therefore, the total sample size for analyses using any data collected after the age of seven years is therefore 15,247 pregnancies, resulting in 15,458 fetuses with 14,775 live births and 14,701 alive children at 1 year of age. Table E1 provides a comparison between characteristics of ALSPAC singleton children and one child of twin births who are alive at age 1 year (n=14,505) with study population (n=9,621). The ALSPAC study website contains details of all data through a fully searchable data dictionary that is available on the following Web page:

http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/

SITAR model for pubertal height growth in ALSPAC

The SuperImposition by Translation And Rotation (SITAR) model fits a single growth curve, summarizing height growth around the time of puberty, which can be applied to all subjects by estimating three subject-specific parameters reflecting translations and rotations of the individual subject growth curves to fit the mean growth curve (2).

The SITAR model can be viewed as follows:

$$y_{it} = a_i + s[(t - b_i)\, e^{c_i}],$$

where y_{it} is height for subject i at age t, whilst $a_i, b_i \; and \; c_i$ are three subject-specific parameters for subject i, and $s[.]$ is a cubic spline curve, with degrees of freedom (df) selected to minimize the Bayesian Information Criterion (df = 4, for both models of male and female subjects), whereas e refers to the natural exponent. The subject-specific parameters $a_i, b_i \; and \; c_i$ can be interpreted as follows:

- a_i is the difference between height of subject i and the overall mean height, measured in units of centimetres. It represents the 'size' parameter for subject i, depicted by an up-down shift (translation) of the mean curve on the height scale, with a_i greater for taller subjects.
- b_i is the difference between pubertal age (APV) of subject i and the overall mean APV, measured in years, and then indicates the 'timing' of subject i at which peak velocity of height is attained. Geometrically, it corresponds to a right-left shift of the mean curve on the age scale, with b_i greater for subjects with later puberty.
- c_i represents the 'velocity' of growth spurt for subject i. It can be illustrated by a stretching or shrinking of the age scale, which results in decreasing or increasing the slope, i.e. velocity, respectively (in other words, rotating the mean curve). Thus, c_i is greater for subjects with rapid spurt and a steeper growth curve.

The SITAR summarizes the departure of each individual growth curve from the mean curve in terms of these three subject-specific parameters, which were estimated and utilised to derive the pubertal age (APV) and peak velocity of pubertal height growth (PV) for each individual. The percentage of between-subjects variability in height growth explained by the SITAR model was obtained by comparing the mixed-effects model incorporating the subject-specific (i.e., random effects) parameters with the model fitting fixed effects parameters only, representing mean growth with no information on individual-level growth trajectories (Table E2).

Data sources

Longitudinal data were collected from several sources: self-administered questionnaires sent every 6 months from birth to age 7 years and every 12 months thereafter; annual physical examinations carried out during research clinics from age 7 to 13 years and at 15, 17 and 24 years.

Self-reported asthma symptoms at ages 16 and 23 years were defined as asthma ever together with a positive answer to either “Have you had any wheezing or whistling in the past 12 months? or "Have you ever had asthma in the past 12 months?" or “Have you been prescribed any asthma medication in the last 12 months? Controls were individuals who answered ‘no’ at all questions. Whereas, self-reported wheezing at ages 16 and 23 years were defined as the positive answer to the question “Have you had any wheezing or whistling in the past 12 months?”.

Potential confounders

Anthropometric, sociodemographic and lifestyle factors were collected at several phases of the study. Data on maternal educational attainment, parental occupational social class, maternal history of asthma or allergy and maternal smoking and anxiety during pregnancy were obtained from questionnaires sent to mothers during pregnancy (3). At birth, delivery health care records provided data on sex, birthweight, gestational period, age of mother at delivery and having at least one sibling (parity). Postnatal maternal questionnaires were used to obtain environmental tobacco smoke exposure (4). From questionnaires at 14 to 23 years, we obtained data on smoking status and ever doctor-diagnosed asthma.

We considered as potential confounders factors that had a consistent evidence in the literature and factors associated with pubertal growth as well as at least one of the lung function measures. Associations of potential confounders with lung function outcomes were examined using multiple linear regression models (Table E5). We identified the following variables as being associated with at least one of the lung function measures and adjusted for them in subsequent analyses: parity (≥ 1 sibling); maternal history of asthma or allergy; maternal smoking during pregnancy; birth weight; ever doctor-diagnosed asthma by age 14 years; exposure to tobacco smoke from birth to 8 years of age; smoking status at 14 years.

Missing lung function data

Missing lung function data at each timepoint were depicted in Figure E1. To assess whether data of lung function were missing at random, we examined the association of lung function measurements at age 8 years with status of data (being measured or missed) at age 15 years; and the association of measurements at age 15 years with status of data at age 24 years by using logistic regression models adjusted for gender, age and height at measurements, see Table E4. In addition, we compared distributions of APV and PV for subjects with and without measured lung function at ages 15 and 24 years, see Figures E2 and E3.

Statistical analyses

The associations of pubertal age (APV) and magnitude of peak height velocity (PV) with lung function outcomes in adolescence and early adulthood were examined by using multivariable linear regression models adjusted for confounders, lung function at age 8 years, age and height at clinic visits for spirometry. We estimated differences in lung functions at age 15 and 24 years associated with 1-year increase in APV, and 1cm/year

increase in PV, mutually adjusted for each other. Relative importance of each of the pubertal height growth predictors (APV and PV) were estimated using the Lindeman, Merenda, and Gold (LMG) method by which proportions of R^2 attributed to each predictor were calculated (5).

We estimated odds of risk for asthma symptoms and wheezing at ages 16 and 23 years associated with 1-year increase in APV, and 1cm/year increase in PV by using logistic regression models adjusted for confounders.

Figure E4 gives an example, using the derived male mean curves, illustrating the way in which a subject-specific height and velocity curves are shifted or rotated, in relation to the mean curve, due to a 1-unit increase in APV or PV respectively. Although the female mean curves are different, the interpretation demonstrated by Figure E4 would be the same.

Secondary analyses

The following secondary analyses were performed to address the robustness of our findings: (1) pre-bronchodilator (pre-BD) measurements were used as lung function outcomes (Table E8); (2) secondary sexual characteristics including age at menarche for females and pubic hair development for males were used as measures of pubertal status (Table 3 in the main manuscript). Data on age at menarche and pubic hair development were obtained from annual maternal and self-reported questionnaires. The respondent was asked to report age at first day of the first menstrual bleeding, and to examine line drawings representing the five Tanner stages for pubic hair and to record the most closely drawing represented the

participant's current stage of development, for female and male subjects respectively. Girls who reported achieving menarche on a questionnaire but reported not yet having their first period on a subsequent questionnaire, were excluded. When more than one age at menarche was given at different questionnaires, the first reported age at menarche was used for analysis. When reported age at menarche was greater than age at questionnaire completion, it was treated as missing. Boys who reported a certain Tanner stage of pubic hair development on one questionnaire then reported a lower stage on a subsequent questionnaire were excluded from these analyses. We analysed the pubic hair Tanner staging interval-censored data using parametric survival models (6) to estimate age at attainment of Tanner stage > 2, which was considered as a proxy for sexual development in males; (3) post- bronchodilator (post-BD) lung function excluding the lowest and highest 1% of measurements were used to examine the sensitivity to extreme spirometry values (Table E9); (4) We performed k-means cluster analysis to identify groups of subjects with similar pubertal growth in terms of timing and intensity (Figure E5). The associations with lung function were then examined using clusters of pubertal patterns to assess pattern-specific differential risks (Figure E6); (5) a sensitivity analysis was performed to investigate the association between lung function at 8 years old and pubertal growth to assess whether lung function in childhood was affecting puberty (Table E10); (6) an analysis restricted to subjects with complete lung function data at ages 8, 15 and 24 years was performed to examine sensitivity to incomplete lung function cases (Table E11).

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TABLES

Table E1. Comparisons for characteristics of subjects in study population and whole ALSPAC population.

Characteristic	Study population ($n_1 = 9,621$)		ALSPAC population† ($n_2 = 14,505$)		*P*‡
	n	Percent or median (IQR)	n	Percent or median (IQR)	
Female	9,621	50.4	14,505	48.7	0.010
Lower maternal education*	8,582	59.6	12,267	64.6	2×10^{-13}
Maternal smoking during pregnancy	8,509	22.8	12,171	29.5	2×10^{-16}
Low birth weight (<2.5 kg)	8,919	4.5	13,628	4.9	0.099
Preterm delivery (<37 wk)	9,032	5.3	13,804	5.6	0.367
Maternal age at delivery (years)	9,032	29.0 (26.0 to 32.0)	13,798	28.0 (25.0 to 31.0)	2×10^{-16}

Abbreviations: IQR = Interquartile range; kg = kilogram; wk = weeks.

*Educated to the General Certificate of Education level (school-leaving certificate) or lower.

†ALSPAC singleton and one child of twin births, alive at age 1 year.

‡*P*-value from the Chi-squared or Mann Whitney test.

Table E2. Summary statistics of height measurements and fitted SITAR models for height growth

	Males	Females
Measurements of height:		
Number of subjects	4,772	4,849
Total of height measurements	33,367	33,783
Median (IQR) number of measurements per subject	8 (4 to 9)	8 (5 to 9)
Range of number of measured heights per subject	1 to 20	1 to 18
Growth models:		
Variance explained (%)*	96.16	96.60
Residual SD (mm)	13.4	11.7
Median (IQR) of APV (years)	13.5 (13.0 to 13.9)	11.7 (11.2 to 12.1)
Median (IQR) of PV (cm/year)	9.9 (9.3 to 10.5)	8.0 (7.5 to 8.5)
Correlation (APV, PV)	- 0.70	- 0.62

Abbreviations: SITAR = superimposition by translation and rotation; IQR = interquartile range; SD = standard deviation; APV = pubertal age; PV = peak velocity; mm = millimetre; cm = centimetre.
*Compared to fixed effects model.

Table E3. Summary statistics for SITAR model's random effect parameters of height growth

Growth random effect	Males			Females		
	SD	Correlation		SD	Correlation	
a: Size (cm)	6.72	*a: Size*	*b: Timing*	6.10	*a: Size*	*b: Timing*
b: Timing (years)	0.89	0.29		0.84	0.31	
c: Velocity (fractional)	0.11	0.29	- 0.59	0.12	0.20	- 0.55

Abbreviations: SD = Standard deviation.

Table E4. Adjusted* associations of lung function measurements at ages 8 and 15 years with data status (missing/measured) at ages 15 and 24 years respectively.

Lung function measurements at age 8 y	Lung function data status† at age 15 y		Lung function measurements at age 15 y	Lung function data status† at age 24 y	
	***β* (95% CI)**	***P*‡**		***β* (95% CI)**	***P*‡**
FEV_1 (µl)	0.04 (-0.2 to 0.3)	0.715	FEV_1 (µl)	-0.03 (-0.1 to 0.08)	0.595
FVC (µl)	0.03 (-0.1 to 0.2)	0.797	FVC (µl)	0.05 (-0.04 to 0.1)	0.291
FEV_1/FVC (%)	-0.22 (-0.98 to 0.54)	0.573	FEV_1/FVC (%)	-0.81 (-1.63 to 0.005)	0.052
FEF_{25-75} (µl/s)	-0.01 (-0.1 to 0.08)	0.796	FEF_{25-75} (µl/s)	-0.05 (-0.1 to 0.008)	0.091

Abbreviations: y = years; µl = microlitre; s = second; β = estimate of effect of 1-unit increase in lung function parameter on probability of lung function being missed at the following timepoint using logistic regression model; CI = confidence interval.

*Adjusted for gender, age and height at lung function measurements.

† 'Measured' data were considered as the reference status in logistic regression models.

‡ *P*-values from Wald test.

Table E5. Associations of possible confounders with lung function outcomes at age 24 years.

	FEV_1 (ml)		FVC (ml)		FEF_{25-75} (ml/s)	
	β **(95% CI)**	***P*§**	***β*** **(95% CI)**	***P*§**	***β*** **(95% CI)**	***P*§**
Demographic, maternal, pregnancy, and subject characteristics (adjusted by each other)						
Female sex	-564 (-622 to -506)	2×10^{-16}	-807(-875 to -740)	2×10^{-16}	-406 (-527 to -285)	6×10^{-11}
Maternal lower education level*	-32.5 (-72.3 to 7.2)	0.109	-15.0 (-61.2 to 31.1)	0.523	-52.3 (-135.1 to 30.5)	0.216
Parity	65.3 (26.4 to 104)	9×10^{-4}	63.3 (18.1 to 108.4)	0.006	80.2 (-0.87 to 161.2)	0.053
Maternal history of asthma or allergy	11.9 (-27.0 to 51.0)	0.547	18.5 (-26.8 to 63.8)	0.424	0.83 (-80.5 to 82.1)	0.984
Maternal smoking during pregnancy	45.3 (-10.0 to 100.6)	0.109	99.9 (35.6 to 164.2)	0.002	-52.7 (-168.0 to 62.7)	0.370
Maternal anxiety during pregnancy†	-30.6 (-74.6 to 13.4)	0.173	-20.1 (-71.3 to 31.0)	0.440	-12.3 (-104.1 to 79.5)	0.793
Prenatal characteristics adjusted by demographic, maternal, pregnancy, and subject characteristics						
Birth weight (kg)‡	99.3 (54.1 to 144.5)	2×10^{-5}	109.0 (56.1 to 161.8)	5×10^{-5}	114.5 (19.9 to 209.1)	0.017
Preterm delivery (<37 wk)	-83.3 (-177.8 to 11.2)	0.084	-35.0 (-144.9 to 74.9)	0.532	-318.3 (-514 to -121.6)	0.001
Postnatal characteristics adjusted by demographic, maternal, pregnancy, subject and prenatal characteristics						
Ever doctor-diagnosed asthma by age 14 y	-43.1 (-96.7 to 10.5)	0.115	18.8 (-44.7 to 82.4)	0.561	-185.1 (-293.1 to -77.1)	0.001
Day care attendance within first year	57.2 (-25.8 to 140.1)	0.177	33.2 (-64.3 to 130.6)	0.504	111.7 (-57.8 to 281.1)	0.196
Exposure to smoke from birth to age 8 y	17.9 (-32.5 to 68.2)	0.487	27.1 (-32.3 to 86.5)	0.371	0.5 (-101.8 to 102.7)	0.993
Smoking by 14 y	47.1 (-13.0 to 107.2)	0.124	98.2 (27.3 to 169.0)	0.007	-26.9 (-148.1 to 94.4)	0.664
Smoking by 23 y	68.5 (20.1 to 116)	0.005	77.1 (22.4 to 131.9)	0.006	51.1 (-47.3 to 149.4)	0.309

Abbreviations: *β* = estimate of regression coefficient; CI = confidence interval; ml = millilitre; s = second; kg = kilogram; wk = weeks; y = years.

*Educated to school-leaving certificate at 16 years (General Certificate of Education level) or lower.

†Anxious mothers were defined as being in the fourth quartile of the Crown-Crisp Experiential Index (7).

‡ Birth weight was additionally adjusted by preterm delivery because gestational age might influence birth weight.

§ *P*-values from Wald test.

Table E6. Crude and adjusted associations of pubertal age and lung function measurements at 15 years and 24 years by sex.

Lung function outcomes	Crude associations				Adjusted* Associations					
	Males		Females		Males			Females		
	***β* (95% CI)**	***P*†**	***β* (95% CI)**	***P*†**	***β* (95% CI)**	***P*†**	**RI‡**	***β* (95% CI)**	***P*†**	**RI‡**
Adolescence (age 15 y):										
FEV_1 (ml)	-45 (-101 to 11)	0.112	50 (-2 to 102)	0.057	-100 (-150 to -50)	8×10^{-5}	0.46	45 (-8 to 98)	0.093	0.32
FVC (ml)	-46 (-108 to 17)	0.150	40 (-14 to 94)	0.145	-103 (-158 to -49)	2×10^{-4}	0.49	40 (-14 to 93)	0.144	0.29
FEV_1/FVC (%)	-0.4 (-1 to 0.2)	0.225	0.5 (-0.1 to 1.1)	0.119	-0.48 (-1 to 0.05)	0.073	0.47	0.5 (-0.1 to 1.1)	0.114	**0.55**
FEF_{25-75} (ml/s)	-109 (-201 to -16)	0.022	62 (-28 to 151)	0.177	-168 (-250 to -86)	6×10^{-5}	0.48	22 (-68 to 111)	0.635	0.30
Early adulthood (age 24 y):										
FEV_1 (ml)	417 (338 to 497)	6×10^{-23}	127 (83 to 171)	1×10^{-8}	263 (180 to 346)	1×10^{-9}	**0.76**	100 (59 to 141)	1×10^{-6}	**0.84**
FVC (ml)	480 (387 to 573)	2×10^{-22}	139 (86 to 191)	3×10^{-7}	263 (167 to 360)	1×10^{-7}	**0.78**	100 (50 to 150)	8×10^{-5}	**0.84**
FEV_1/FVC (%)	0.3 (-0.6 to 1.1)	0.528	0.2 (-0.4 to 0.7)	0.519	0.5 (-0.4 to 1.4)	0.273	0.46	0.1 (-0.4 to 0.7)	0.601	**0.82**
FEF_{25-75} (ml/s)	355 (205 to 504)	4×10^{-6}	57 (-25 to 139)	0.171	270 (114 to 425)	7×10^{-4}	**0.77**	41 (-38 to 121)	0.309	**0.59**

Abbreviations: *β* = estimate of effect of 1-year increase in pubertal age on lung function; CI = confidence interval; RI = relative importance of pubertal age compared to peak height velocity; y = years, ml = millilitre; s = second.

*Adjusted for: lung function at age 8 years; age and height at visit clinics in which lung function outcomes were measures (at age 15 and 24 years); parity; maternal history of asthma or allergy; maternal smoking during pregnancy; preterm delivery; ever doctor-diagnosed asthma by age 14 years; exposure to smoke from birth to 8 years of age; smoking status.

†*P*-values from Wald test.

‡RI obtained using Lindeman, Merenda, and Gold (LMG) method(5). It estimates the relative importance of pubertal age compared to peak height velocity as the proportion of R^2 decomposition attributed to the pubertal age. RI values greater than 0.5 (highlighted in bold blue) indicate more importance of the pubertal age compared with peak velocity.

Table E7. Crude and adjusted associations of peak velocity of pubertal height growth and lung function measurements at 15 years and 24 years by sex.

Lung function outcomes	Crude associations				Adjusted* Associations					
	Males		Females		Males			Females		
	***β* (95% CI)**	***P*†**	***β* (95% CI)**	***P*†**	***β* (95% CI)**	***P*†**	**RI‡**	***β* (95% CI)**	***P*†**	**RI‡**
Adolescence (age 15 y):										
FEV_1 (ml)	367 (317 to 416)	5×10^{-44}	152 (103 to 202)	2×10^{-9}	143 (85 to 201)	2×10^{-6}	**0.54**	56 (4 to 108)	0.034	**0.68**
FVC (ml)	380 (324 to 435)	1×10^{-38}	169 (117 to 220)	1×10^{-10}	129 (64 to 193)	9×10^{-5}	**0.51**	51 (-1 to 103)	0.054	**0.71**
FEV_1/FVC (%)	0.5 (0 to 1)	0.057	-0.1 (-0.4 to 0.7)	0.657	0.6 (0.02 to 1.2)	0.043	**0.53**	0.5 (-0.2 to 1.1)	0.138	0.45
FEF_{25-75} (ml/s)	414 (332 to 497)	3×10^{-22}	136 (51 to 221)	0.002	220 (124 to 315)	8×10^{-6}	**0.52**	28 (-62 to 119)	0.540	**0.70**
Early adulthood (age 24 y):										
FEV_1 (ml)	388 (319 to 457)	9×10^{-26}	134 (92 to 176)	6×10^{-10}	161 (85 to 237)	4×10^{-5}	0.24	46 (6 to 86)	0.025	0.16
FVC (ml)	452 (372 to 533)	8×10^{-26}	169 (118 to 219)	8×10^{-11}	145 (56 to 234)	0.001	0.22	50 (2 to 99)	0.043	0.16
FEV_1/FVC (%)	0.2 (-0.6 to 1)	0.688	-0.2 (-0.7 to 0.3)	0.402	0.5 (-0.4 to 1.4)	0.294	**0.54**	0 (-0.5 to 0.6)	0.903	0.18
FEF_{25-75} (ml/s)	329 (199 to 458)	9×10^{-7}	38 (-41 to 116)	0.350	163 (17 to 308)	0.029	0.23	-20 (-97 to 57)	0.613	0.41

Abbreviations: β = estimate of effect of 1-cm/year increase in peak height velocity on lung function; CI = confidence interval; RI = relative importance of peak height velocity compared to pubertal age; y = years; ml = millilitre; s = second.

*Adjusted for: lung function at age 8 years; age and height at visit clinics in which lung function outcomes were measures (at age 15 and 24 years); parity; maternal history of asthma or allergy; maternal smoking during pregnancy; preterm delivery; ever doctor-diagnosed asthma by age 14 years; exposure to smoke from birth to 8 years of age; smoking status.

†*P*-values from Wald test.

‡RI obtained using Lindeman, Merenda, and Gold (LMG) method(5). It estimates the relative importance of peak height velocity compared to pubertal age as the proportion of R^2 decomposition attributed to the peak velocity. RI values greater than 0.5 (highlighted in bold blue) indicate more importance of the peak velocity compared with pubertal age.

Table E8. Adjusted* associations of pubertal age (APV) and magnitude of peak height velocity (PV) with prebronchodilator lung function measurements at 15 years and 24 years by sex

Lung function outcomes	Pubertal age (APV)				Peak velocity (PV)			
	Males		Females		Males		Females	
	β (95% CI)	P†	β (95% CI)	P†	β (95% CI)	P†	β (95% CI)	P†
Adolescence (age 15 y):	**($n_1 = 1{,}311$)**		**($n_2 = 1{,}390$)**		**($n_1 = 1{,}311$)**		**($n_2 = 1{,}390$)**	
FEV_1 (ml)	-95 (-140 to -50)	3×10^{-5}	68 (25 to 212)	0.002	144 (90 to 197)	1×10^{-7}	58 (16 to 100)	0.007
FVC (ml)	-87 (-137 to -37)	7×10^{-4}	34 (-12 to 81)	0.148	136 (76 to 195)	8×10^{-6}	34 (-10 to 79)	0.133
FEV_1/FVC (%)	-0.6 (-1.2 to -0.1)	0.021	0.7 (0.1 to 1.2)	0.031	0.1 (-0.5 to 0.7)	0.715	0.7 (0.1 to 1.3)	0.020
FEF_{25-75} (ml/s)	-173 (-245 to -101)	2×10^{-6}	80 (8 to 151)	0.030	128 (44 to 212)	0.003	65 (-7 to 137)	0.079
Early adulthood (age 24 y):	**($n_1 = 724$)**		**($n_2 = 1{,}200$)**		**($n_1 = 724$)**		**($n_2 = 1{,}200$)**	
FEV_1 (ml)	264 (180 to 348)	1×10^{-9}	143 (105 to 182)	7×10^{-13}	178 (101 to 255)	7×10^{-6}	46 (11 to 81)	0.010
FVC (ml)	301 (202 to 400)	4×10^{-9}	119 (71 to 167)	1×10^{-6}	218 (127 to 310)	4×10^{-6}	43 (0 to 87)	0.049
FEV_1/FVC (%)	0.1 (-0.9 to 1.1)	0.830	0.3 (-0.3 to 0.9)	0.278	-0.1 (-1.1 to 0.8)	0.795	-0.1 (-0.7 to 0.4)	0.645
FEF_{25-75} (ml/s)	235 (87 to 383)	0.002	143 (70 to 216)	1×10^{-4}	126 (-14 to 265)	0.078	18 (-52 to 88)	0.615

Abbreviations: β = estimate of effect of 1-year increase in APV or 1-cm/year increase in PV on lung function; CI = confidence interval; y = years; ml = millilitre; s = second.

*Adjusted for: lung function at age 8 years; age and height at clinic visits for spirometry; parity; maternal history of asthma or allergy; maternal smoking during pregnancy; preterm delivery; ever doctor-diagnosed asthma by age 14 years; exposure to smoke from birth to 8 years of age; smoking status.

†P-values from Wald test.

Table E9. Adjusted* associations of pubertal age and magnitude of peak height velocity with lung function measurements at age 15 and 24 years, excluding lowest and highest 1% of spirometry, by sex.

Lung function outcomes	Pubertal age (APV)				Peak velocity (PV)			
	Males		Females		Males		Females	
	β (95% CI)	P†	β (95% CI)	P†	β (95% CI)	P†	β (95% CI)	P†
Adolescence (age 15 y):	**(n_1 = 1,152)**		**(n_2 = 1,212)**		**(n_1 = 1,152)**		**(n_2 = 1,212)**	
FEV_1 (ml)	-107 (-154 to -61)	5×10^{-6}	41 (-7 to 89)	0.094	118 (63 to 173)	2×10^{-5}	51 (4 to 98)	0.033
FVC (ml)	-100 (-151 to -49)	1×10^{-4}	38 (-12 to 87)	0.136	97 (36 to 158)	0.002	49 (1 to 97)	0.044
FEV_1/FVC (%)	-0.4 (-0.9 to 0.1)	0.077	0.6 (0.1 to 1.1)	0.034	0.5 (-0.1 to 1.1)	0.076	0.4 (-0.2 to 0.9)	0.177
FEF_{25-75} (ml/s)	-171 (-248 to -94)	1×10^{-5}	22 (-62 to 106)	0.612	192 (101 to 282)	4×10^{-5}	10 (-74 to 94)	0.813
Early adulthood (age 24 y):	**(n_1 = 553)**		**(n_2 = 980)**		**(n_1 = 553)**		**(n_2 = 980)**	
FEV_1 (ml)	220 (131 to 308)	2×10^{-6}	103 (62 to 144)	8×10^{-7}	127 (44 to 209)	0.003	33 (-4 to 70)	0.078
FVC (ml)	215 (110 to 320)	7×10^{-5}	98 (48 to 147)	1×10^{-4}	106 (9 to 204)	0.032	28 (-16 to 73)	0.214
FEV_1/FVC (%)	1 (0.1 to 1.8)	0.034	0.1 (-0.4 to 0.6)	0.630	0.8 (-0.1 to 1.6)	0.075	0.1 (-0.5 to 0.6)	0.856
FEF_{25-75} (ml/s)	298 (152 to 445)	7×10^{-5}	80 (3 to 158)	0.042	206 (67 to 345)	0.004	2 (-72 to 76)	0.960

Abbreviations: β = estimate of effect of 1-year increase in pubertal age or 1-cm/year increase in magnitude of peak height velocity on lung function; CI = confidence interval; y = years; ml = millilitre; s = second.

*Adjusted for: lung function at age 8 years; age and height at clinic visits for spirometry; parity; maternal history of asthma or allergy; maternal smoking during pregnancy; preterm delivery; ever doctor-diagnosed asthma by age 14 years; exposure to smoke from birth to 8 years of age; smoking status.

†P-values from Wald test.

Table E10. Adjusted* associations of lung function at age 8 years with pubertal age (APV) and peak height velocity (PV), by sex.

Pubertal height growth	Lung function at age 8 years							
	FEV_1		**FVC**		**FEV_1/FVC**		**FEF_{25-75}**	
	β (95% CI)	***P*†**	**β (95% CI)**	***P*†**	**β (95% CI)**	***P*†**	**β (95% CI)**	***P*†**
Males	**($n_1 = 2{,}507$)**		**($n_1 = 2{,}538$)**		**($n_1 = 2{,}507$)**		**($n_1 = 2{,}538$)**	
APV (years)	0 (-9×10^{-5} to 2×10^{-4})	0.507	0 (-1×10^{-4} to 1×10^{-4})	0.934	0.3 (-0.2 to 0.8)	0.214	0 (-4×10^{-5} to 8×10^{-5})	0.581
PV (cm/year)	0 (-1×10^{-4} to 2×10^{-4})	0.785	0 (-1×10^{-4} to 2×10^{-4})	0.699	-0.2 (-0.7 to 0.3)	0.401	0 (-7×10^{-5} to 6×10^{-5})	0.880
Females	**($n_2 = 2{,}484$)**		**($n_2 = 2{,}530$)**		**($n_2 = 2{,}483$)**		**($n_2 = 2{,}530$)**	
APV (years)	0 (-2×10^{-4} to 9×10^{-5})	0.437	0 (-2×10^{-4} to 1×10^{-5})	0.082	-0.3 (-0.1 to 0.8)	0.163	0 (-6×10^{-5} to 5×10^{-5})	0.821
PV (cm/year)	0 (-2×10^{-4} to 1×10^{-4})	0.721	0 (-1×10^{-4} to 1×10^{-4})	0.959	-0.1 (-0.6 to 0.5)	0.785	0 (-8×10^{-5} to 5×10^{-5})	0.735

Abbreviations: APV = pubertal age; PV = peak velocity; β = estimate of effect of 1-unit increase in lung function (millilitre for FEV_1 and FVC, percent for FEV_1/FVC, and millilitre/second for FEF_{25-75}) on pubertal height growth; CI = confidence interval.

*Adjusted for: age and height at clinic visit at age 8 years; parity; maternal history of asthma or allergy; maternal smoking during pregnancy; preterm delivery; exposure to smoke from birth to 8 years of age.

†*P*-values from Wald test.

Table E11. Adjusted* associations of pubertal age (APV) and magnitude of peak height velocity (PV) with postbronchodilator lung function measurements at 15 years and 24 years by sex, restricted to subjects with complete lung function data at ages 8,15 and 24 years.

Lung function outcomes	Pubertal age (APV)				Peak velocity (PV)			
	Males		Females		Males		Females	
	β (95% CI)	P†	β (95% CI)	P†	β (95% CI)	P†	β (95% CI)	P†
Adolescence (age 15 y):	**($n_1 = 451$)**		**($n_2 = 707$)**		**($n_1 = 451$)**		**($n_2 = 707$)**	
FEV_1 (ml)	-87 (-169 to -5)	0.038	58 (-11 to 127)	0.099	150 (53 to 247)	0.003	54 (-14 to 122)	0.119
FVC (ml)	-93 (-183 to -2)	0.044	45 (-27 to 116)	0.219	126 (19 to 234)	0.021	39 (-31 to 108)	0.273
FEV_1/FVC (%)	-0.5 (-1.3 to 0.4)	0.256	0.3 (-0.5 to 1.1)	0.479	0.8 (-0.2 to 1.8)	0.102	0.3 (-0.6 to 1.1)	0.556
FEF_{25-75} (ml/s)	-108 (-241 to 24)	0.108	-8 (-125 to 108)	0.886	284 (128 to 440)	4×10^{-4}	-7 (-126 to 112)	0.907
Early adulthood (age 24 y):	**($n_1 = 451$)**		**($n_2 = 707$)**		**($n_1 = 451$)**		**($n_2 = 707$)**	
FEV_1 (ml)	282 (181 to 382)	6×10^{-8}	99 (33 to 146)	3×10^{-5}	193 (99 to 287)	6×10^{-5}	37 (-8 to 81)	0.105
FVC (ml)	277 (161 to 394)	4×10^{-6}	95 (37 to 153)	0.001	170 (61 to 279)	0.002	34 (-20 to 89)	0.216
FEV_1/FVC (%)	0.7 (-0.4 to 1.8)	0.186	0.2 (-0.4 to 0.8)	0.518	0.8 (-0.3 to 1.8)	0.143	0.1 (-0.5 to 0.7)	0.829
FEF_{25-75} (ml/s)	362 (181 to 543)	1×10^{-4}	65 (-25 to 155)	0.158	267 (93 to 441)	0.003	-9 (-100 to 82)	0.850

Abbreviations: β = estimate of effect of 1-year increase in pubertal age or 1-cm/year increase in magnitude of peak height velocity on lung function; CI = confidence interval; y = years; ml = millilitre; s = second.

*Adjusted for: lung function at age 8 years; age and height at clinic visits for spirometry; parity; maternal history of asthma or allergy; maternal smoking during pregnancy; preterm delivery; ever doctor-diagnosed asthma by age 14 years; exposure to smoke from birth to 8 years of age; smoking status.

†P-values from Wald test.

FIGURES

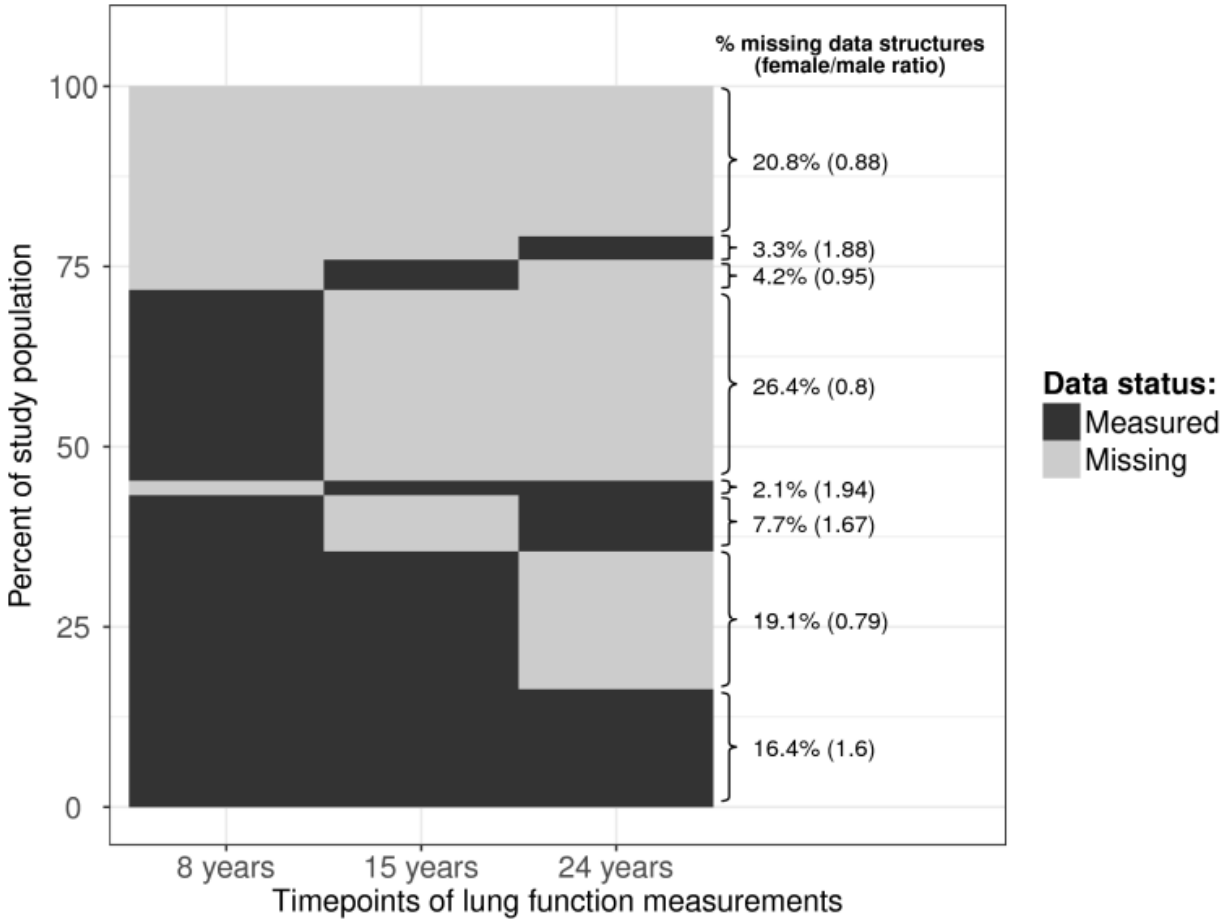

Figure E1. Layout of missing lung function data at ages 8, 15 and 24 years.

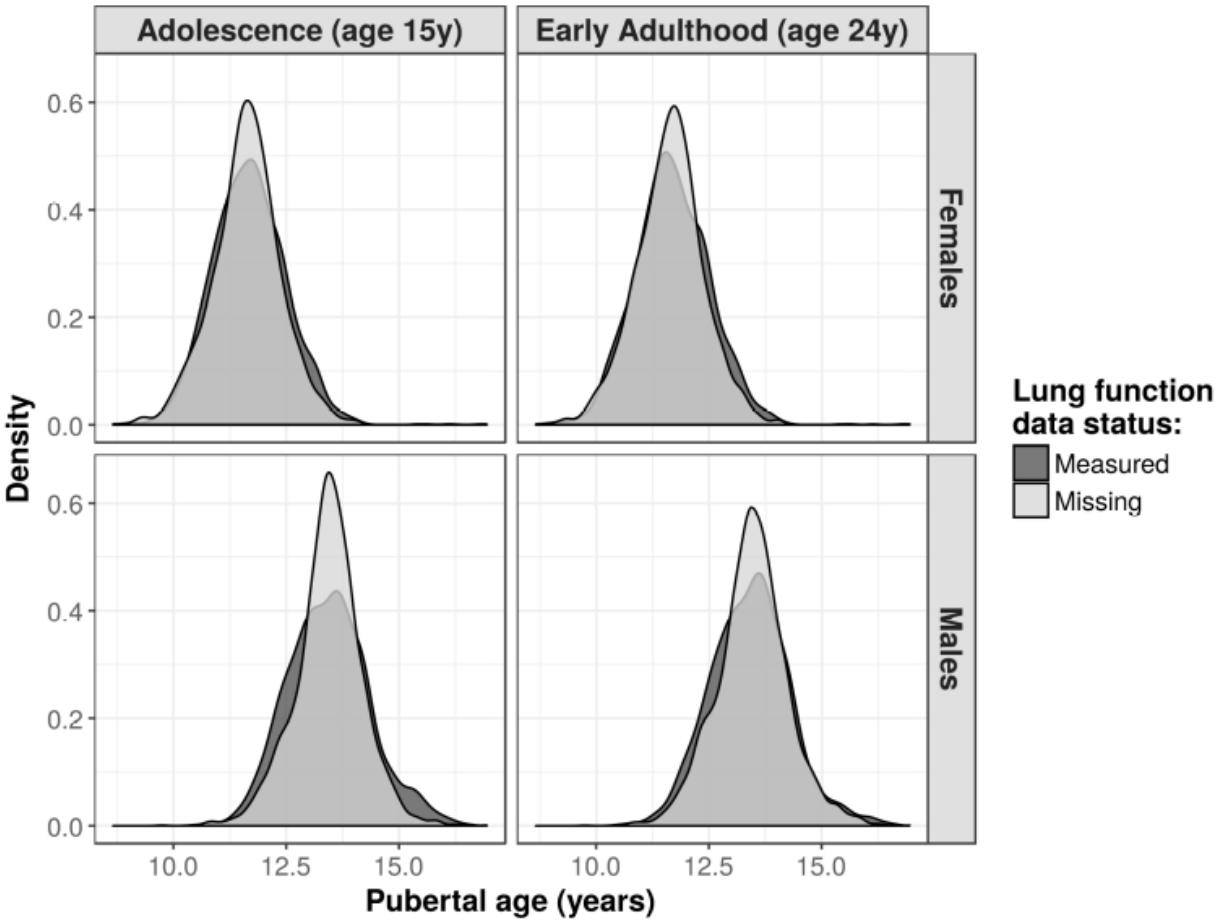

Figure E2. Comparisons of pubertal age (APV) distributions between subjects with and without lung function data measured at ages 15 and 24 years by gender.

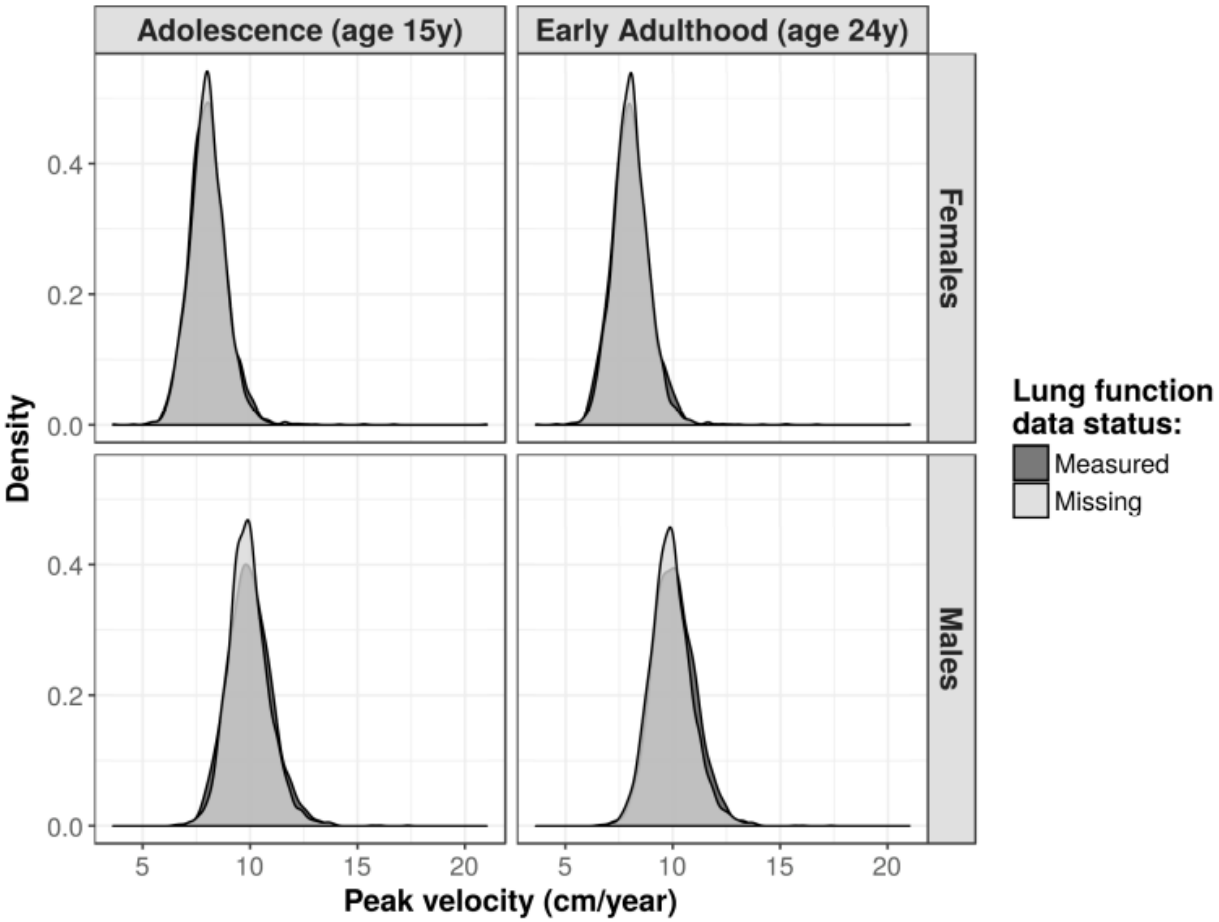

Figure E3. Comparisons of peak height velocity (PV) distributions between subjects with and without lung function data measured at ages 15 and 24 years by gender.

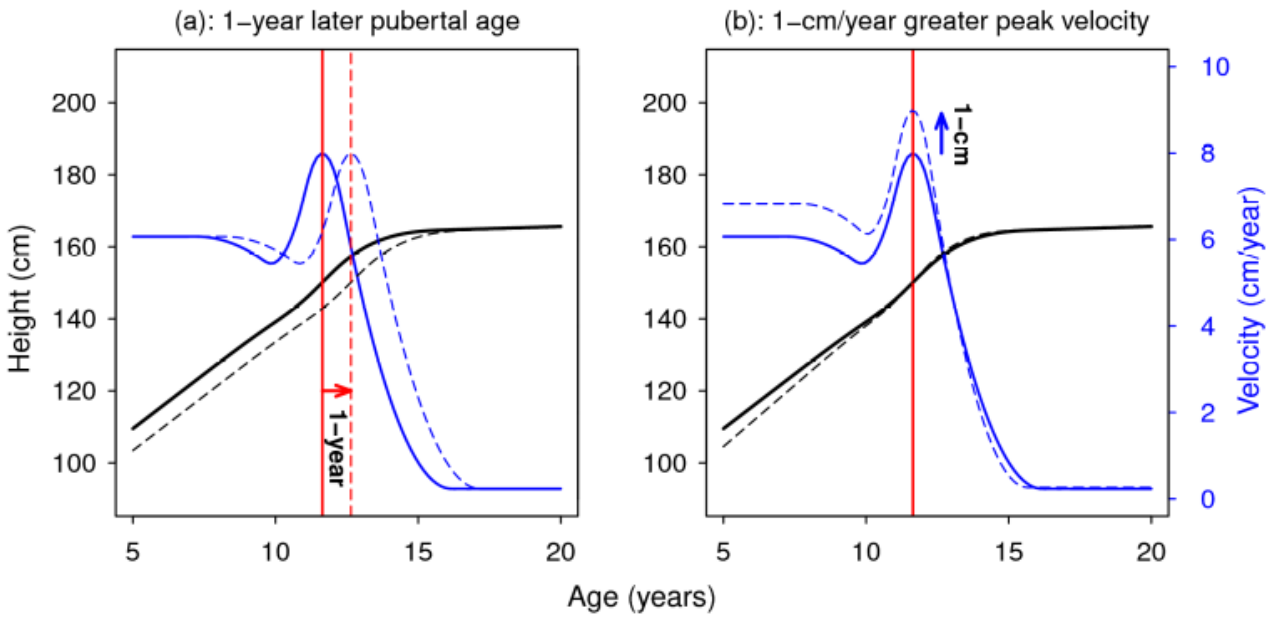

Figure E4. Illustrations of 1-unit increase in: (a) pubertal age, in years; (b) peak velocity, in cm/year, of an individual's pubertal height spurt. The growth curves corresponding to (a) 1-year latter puberty, while other factors remain unchanged; and (b) 1-cm/year greater peak velocity, while other factors remain unchanged, compared with male mean curves (solid lines) were respectively depicted in dashed drawing. The mean curves of males were used as an example of baseline curves for illustration purposes.

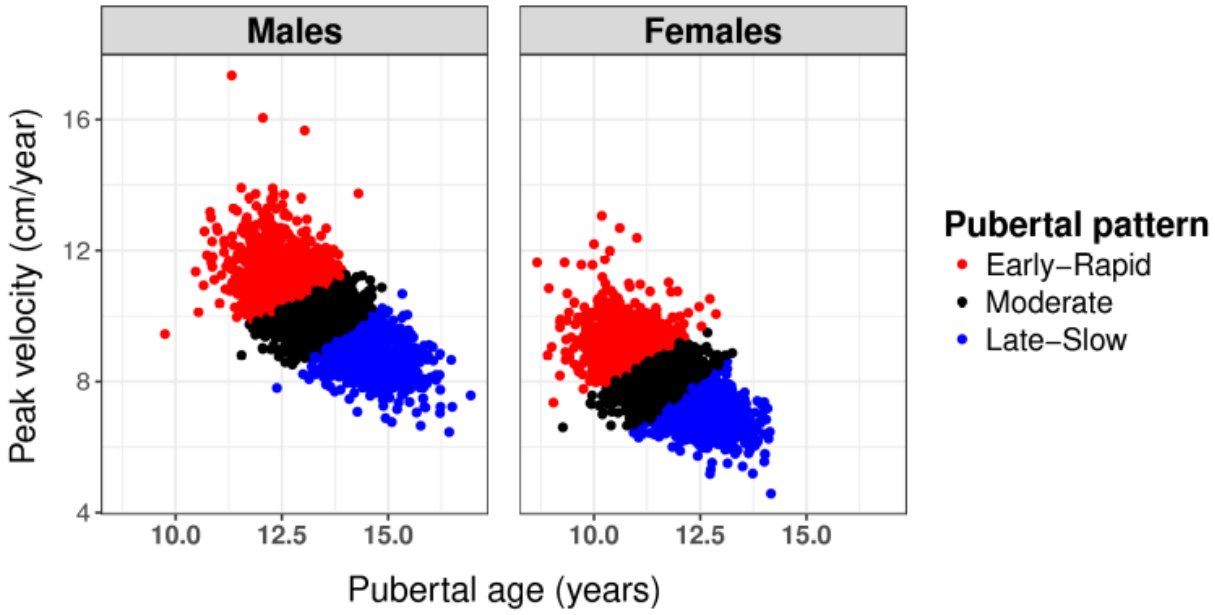

Figure E5. Clusters of pubertal patterns in terms of age and peak velocity of pubertal growth by sex.

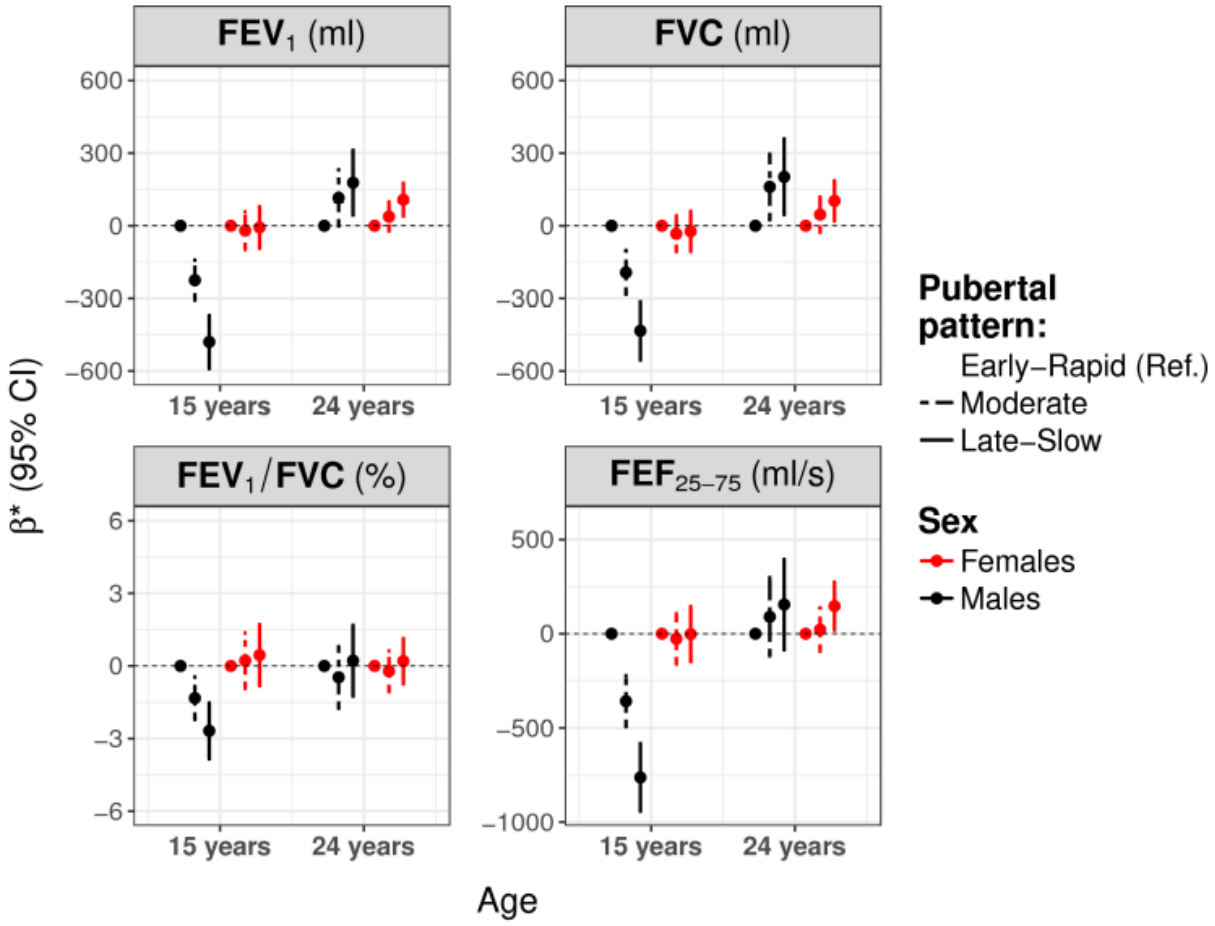

Figure E6. Adjusted associations of pubertal clusters with lung function measurements at age 15 and 24 years by sex.

Abbreviations: β = Adjusted difference in lung function measurement associated with corresponding pubertal pattern compared to the 'Early-rapid' pubertal growth (reference group).

*Adjusted for: lung function at age 8 years; age and height at clinic visits for spirometry; parity; maternal history of asthma or allergy; maternal smoking during pregnancy; preterm delivery; ever doctor-diagnosed asthma by age 14 years; exposure to smoke from birth to 8 years of age; smoking status.