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Pubertal onset with adulthood lung function mediated by height growth in adolescence

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ABSTRACT

Background: Age of pubertal onset is associated with height and lung function in adulthood. It is unknown whether height growth in adolescence mediates the association of age at puberty with early adult lung function.

Methods: Data from the Isle of Wight (IOW) birth cohort (n=1261) were examined in the study. Ages of pubertal events, height at ages 10 and 18 years and lung function parameters (FVC, FEV_1) at 26 years were included in a path analyses to assess the mediation effects of height growth. Findings were tested in the ALSPAC birth cohort.

Results: In females in the IOW cohort, age at menarche and body hair growth showed a positive indirect association with FVC (menarche: indirect effect coefficient [IEC]=0.13, 95% confidence interval [CI]:0.05-0.20, $p=1.28\times10^{-3}$; body hair growth: IEC=0.08, 95% CI: 0.01-0.15, p=0.017) and FEV_1 (menarche: IEC=0.09, 95% CI: 0.01-0.17, p=0.028; body hair growth: IEC=0.07, 95% CI: 0.01-0.14, p=0.043) at 26 years through height growth and lung function at 18 years. In males, age at body hair growth (IEC=0.08; 95% CI: 0.01-0.15, p=0.047), growth spurt (IEC=0.09; 95% CI: 0.01-0.17, p=0.034), and facial hair growth (IEC=0.09; 95% CI: 0.02-0.16, p=0.014) had positive indirect effects on FVC at 26 years, but voice deepening did not show statistically significant indirect effects

(p>0.05). For pubertal events available in the ALSPAC cohort, results consistent with the IOW cohort were found for both females and males.

Conclusion: Effects of age of puberty on FVC in early adulthood are likely mediated by height growth during adolescence.

Keywords: IOW, ALSPAC, Pubertal event, Height growth, Lung function, Path analysis.

Take-home message: Height growth in adolescence mediated the association of age of pubertal onset with FVC in young adults. For females, such mediation effects were also identified for FEV_1.

Introduction

Lung function assessments are often performed to diagnose, monitor, and evaluate disease status and health conditions such as asthma [1], chronic obstructive pulmonary disease (COPD) [2], infectious respiratory disease [3], and lung cancer [4]. Different lung function parameters, e.g., spirometry measures forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), represent different physiological and clinical conditions [5]. Multiple studies have indicated that distinctive patterns of lung function development have substantial implications for health and disease [6-10]. For example, early below average FEV_1 trajectory is associated with increased risk of developing COPD by middle age [8].

Adolescence is an important period accompanied by significant gender-dependent changes, e.g., puberty, rapid growth, and often BMI increase. It is also a critical period for the maturation of lung function [11]. It has been previously shown that age at menarche (in females), body hair growth (in males), and peak height velocity (in both sexes) are associated with lung function in later life [11-15]. For instance, early menarche is associated with better lung function development in adolescence, but the opposite in adulthood [13]. A recent Mendelian randomization study suggested that pubertal timing, rather than specific pubertal events, was associated with lung function in both females and males [13].

Age at puberty is also closely related to height growth during adolescence and this association is potentially gender-dependent. For girls, earlier age at puberty is associated with shorter height, while in boys, earlier age at puberty and slow progression through puberty is linked to taller height in early adulthood [16]. A strong association between height growth during adolescence and lung function in adulthood has been previously observed. Lung function increases with height in adolescence, although the association can be non-linear [17, 18]. However, after adolescence, lung volume continues to increase after adult height reaches a plateau [19, 20]. Recent findings in the ALSPAC cohort indicated that subjects with greater peak velocity of height growth in puberty had higher FVC and FEV_1 in young adulthood [15] and that height growth during adolescence was

associated with age of puberty and with lung function at young adulthood. However, it is unknown whether height growth plays a mediating role in the association of age at puberty with lung function in early adulthood.

The objectives of this study were to test whether height growth during adolescence mediated the association of age at puberty with lung function. We applied path analyses [21] using data in the Isle of Wight (IOW) birth cohort established in 1989/1990 in the United Kingdom [22].

Methods

Study population

A population-based birth cohort study was initiated in 1989 on the Isle of Wight (IOW), UK to prospectively study the natural history of allergic diseases, asthma and lung function and associated risk factors [22]. Of the 1,536 children born and recruited in this period, 1,261 were available for further follow-up with data collected at ages 10, 18, and 26 years (Figure S1). The Local Research Ethics Committee approved this study. Written informed individual or parental consent was contained at in person visits. In addition to demographic information and age of pubertal events collected via questionnaire, at ages 10, 18, and 26 years height and weight were measured, and lung function parameters and allergic conditions were assessed.

Ages of pubertal onset and height growth in adolescence

At 18 years of age, subjects were interviewed to recall the age of onset for pubertal events using questions relating to pubertal events from the National Institute of Child and Human Development (NICHD) [16]. For females, these included questions on body hair growth, breast growth, menarche, skin changes, and growth spurt. Those in males included body hair growth, facial hair growth, voice deepening, skin changes, and growth spurt. The detailed measurements of pubertal events are described elsewhere [16].

Height at ages 10 and 18 years was recorded through standard height measurement; in those who did not attend the clinic the information was acquired by self-report. Height growth was baseline-

adjusted and calculated as change in height from 10 to 18 years (representing pre- to post-adolescence) divided by the height at 10 years. This measure considers the height gain during adolescence adjusted by pre-adolescence height.

Lung function assessment

Assessment of lung function at ages 18 and 26 years of age was conducted by the KoKo spirometry software package on a portable desktop device (PDS instrumentation, Louisville, KY, USS) [23]. Tests were conducted according to the guidelines of the American Thoracic Society and European Respiratory Society [24]. The lung function measurements included in this study were forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1).

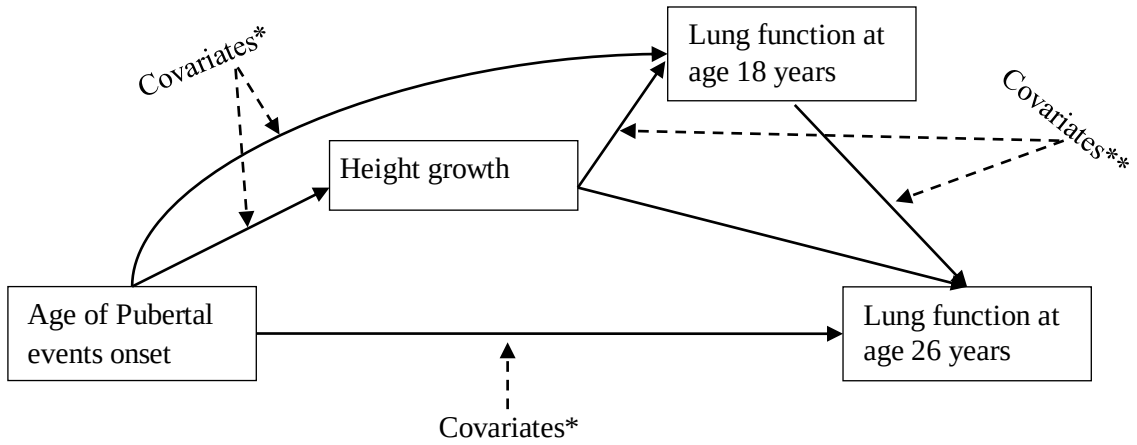
Potential confounders

Factors related to growth, demographic features, and environmental exposure might confound association of age onset of pubertal events with height growth and lung function. In this study, low birth weight status, maternal smoking status during pregnancy, asthma status and body mass index (BMI) at age 10 years, socioeconomic status (SES), and personal smoking status at age 18 years were considered as potential confounders. Birth weight and maternal smoking during pregnancy were obtained at birth of the child. Asthma was defined as having 'physician diagnosed asthma' and either 'wheezing or whistling in the chest in the last 12 months' and/or 'current treatment for asthma', using the ISAAC questionnaire [25]. BMI was defined by weight (kilograms) divided by the square of height (meters). SES was ascertained by 'low', 'medium' and' high' according to assessment of level of household income and number of rooms in the house.

Statistical analyses

Since there are major differences between boys and girls in pubertal events, all data analyses were stratified by gender. To compare samples included in the present study and in the total cohort, one sample t-tests were used on main continuous variables of interest including age of onset of pubertal events, lung function, and height at ages 10 and 18 years.

The direct and indirect effects of age at puberty on lung function measurements (FVC and FEV_1) at ages 18 and 26 years were examined using path analyses via structural equation modeling (SEM) [21, 26]. Height growth was included in the path analyses as a potential mediator (Figure 1). For the purpose of selecting pubertal events to be included in the path analyses, three analyses using linear regressions were conducted; the first two analyses examined the association of age of onset for pubertal events with lung function parameters (FVC and FEV_1) at both ages 18 and 26 years, and the third analyses tested the association of age of onset for pubertal events associated with the lung function parameters at one of the two ages (18 and 26 years) and with height growth were included in the subsequent path analyses (Figure 1), and we performed a path analysis for each of these pubertal events. Path analyses were performed using PROC CALIS in SAS 9.4 (SAS, Cary, NC, USA). A p-value<0.05 was deemed as being statistically significant.



* Asthma status at age 10 years, height at age 10 years, BMI at age 10 years, SES at age 10 years, birth weight status, maternal smoking during pregnancy.
** Smoking at age 18 years.

FIGURE1 The path diagram with two mediators: height growth and lung function at ages 18 years.

Replication cohort

Findings in the IOW birth cohort were further tested in the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, UK [27-29]. ALSPAC is a multi-generational prospective birth cohort study investigating influences on health and development across the life course [27-29]. All

pregnant women residing in and around the city of Bristol (south-west UK) during 1990-1992 were eligible to enroll in the cohort, and 14,062 live newborns were recruited. Data on demographics, ages of puberty onset (menarche and body hair growth for females, and body hair growth for males), height at ages 10 and 17 years, along with lung function parameters FEV_1 and FVC measured at ages 15/17 and 24 years were included in our study. The details of all the data are available on the study website (http://www.bristol.ac.uk/alspac/researchers/our-data/). Ethical approval for the study was obtained from the ALSPAC Ethics and LAW Committee and the Local Research Ethics Committees. Height growth was calculated using height at age 10 and age 17 years. In total, complete data on 2,296 females and 1,409 males were included in the analyses. The same path analyses modeling with comparable covariates were applied and results with p-value <0.05 were treated as being statistically significant.

Results

Characteristics of the Study Population

Using one sample t-tests, we compared the subsamples with complete data on ages of pubertal events onset, lung function measures, and height at ages 10 and 18 years, stratified by gender. No statistically significant differences were identified (all p values ≥ 0.05, Table 1).

TABLE 1 Comparison of the analytical subsample (n=888) with the whole IOW cohort (n=1,261) with regard to age of onset of pubertal event, lung function, and height

Variables	Cohort samples mean±SD n=1261	Subsamples mean±SD n=888	p-value
Age of pubertal events (years)			
Female			
Breast growth	12.43±1.58	12.45±1.58	0.87
Body hair growth	12.25±1.43	12.26±1.41	0.91
Growth spurt	12.52±1.70	12.54±1.70	0.90
Skin changes	13.11±1.50	13.06±1.50	0.55
Menarche	12.72±1.42	12.72±1.37	0.95
Male			
Body hair growth	13.41±1.37	13.28±1.34	0.10
Growth spurt	13.72±1.67	13.58±1.64	0.14

Voice deepening	14.24±1.24	14.14±1.21	0.14
Facial hair growth	15.38±1.16	15.28±1.15	0.11
Skin changes	13.99±1.38	13.97±1.36	0.81
Lung function (litres) (age 26)			
Female			
FVC	4.24±0.54	4.27±0.54	0.32
FEV_1	3.42±0.43	3.44±0.42	0.49
Male			
FVC	5.85±0.82	5.88±0.81	0.58
FEV_1	4.61±0.72	4.63±0.71	0.67
Height (cm)			
Female			
Age 10	139.10±6.47	139.10±6.40	0.92
Age 18	164.70±6.33	164.80±6.17	0.78
Male			
Age 10	139.00±5.89	139.10±5.84	0.74
Age 18	178.20±6.87	177.90±6.63	0.42

Mediation analysis in the IOW cohort

Ages of menarche and body hair growth in females, and body hair growth, growth spurt, voice deepening, and facial hair growth in males were included in the path analyses due to their associations with height growth and lung function at ages 18 or 26 years (Tables S1-S3 in Supplemental material S.2).

For females, significant indirect effects of the age of onset of pubertal events via height growth on the lung function parameters FVC and FEV_1 were detected. After adjusting for confounding factors, path analyses indicated that later menarche had an indirect effect on higher FVC (indirect effect coefficient [IEC]=0.13; 95% confidence interval (CI): 0.05, 0.20; $p=1.28\times10^{-3}$) (Table 2A, Figure S2) and FEV_1 (IEC=0.09; 95% CI: 0.01, 0.17; p=0.028) (Table 2A) via height growth during adolescence and lung function (FVC and FEV_1, respectively) at age 18 years. Similar indirect effects were also seen for later age of body hair growth and higher FVC and FEV_1 at age 26 years (FVC: IEC=0.08; 95% CI: 0.01, 0.15; p=0.017; FEV_1: IEC=0.07; 95% CI: 0.01, 0.14; p=0.043) (Table 2A). For these two pubertal events (menarche and body hair growth), no statistically significant direct effects on FVC at age 26 were observed. For FEV1, there was a significant direct

effect of age at menarche on FEV_1 at 26 years (DEC=0.12; 95% CI: 0.04, 0.20; $p=5.15x10^{-3}$), in addition to its indirect effects (Table 2A).

For males, we identified three pubertal events with similar indirect associations with FVC at age 26, as observed in females (Table 2B), body hair growth (IEC=0.08; 95% CI: 0.01, 0.15; p=0.047), growth spurt (IEC =0.09; 95% CI: 0.01, 0.17; p=0.034), and facial hair growth (IEC=0.09; 95% CI: 0.02, 0.16; p=0.014). For example, after adjusting for other covariates in the analyses, later ages of first body hair growth was associated with larger height growth, which was further associated with higher FVC at ages 18 and/or 26 (Figure S3). Age of facial hair growth also had a significant direct effect on FVC (DEC=0.09; 95% CI: 0.01, 0.16; p=0.026; Table 2B). We did not identify any statistically significant indirect effects for FEV_1 in males.

Replication analyses in the ALSPAC cohort

The statistically significant findings identified in the path analyses in the IOW cohort were further tested in the ALSPAC cohort using lung function measures at ages 15/17 and 24 years. In females, mediation effects of height growth were observed in ALSPAC for all the pubertal events identified in the IOW cohort, with respect to statistical significance as well as directions of association (Table 2A, Figure S4-S6). Later age at menarche was indirectly associated with higher FVC and FEV_1 at age 24 years via height growth and age 15/17 lung function (for FVC, IEC=0.21; 95% CI: 0.17, 0.24; $p<10^{-31}$; and for FEV_1, IEC=0.20; 95% CI: 0.17, 0.24; $p<10^{-31}$, respectively). Comparable effects of the age of body hair growth in females were also observed (Table 2A, Figure S5 and S6). For males, the effects of age at body hair growth were consistent with (but smaller than) those identified in IOW (Table 2B) with statistically significant indirect effects on FVC (IEC=0.04; 95% CI: 0.01, 0.07; p=0.003).

TABLE 2A Statistically significant effects of ages of pubertal events onset on lung function at age 26 years through height growth and lung function at age 18 years in *females* in IOW, further tested in the replication cohort, ALSPAC. For the IOW, only statistically significant results are included in the table

Cohort	Age of onset of Pubertal events	Lung function	Total effect [#]Est. (L); 95% CI	p-value	Direct effect [#]Est. (L); 95% CI	p-value	Indirect effect [#]Est. (L); 95% CI	p-value
IOW	Menarche	FVC	0.18; (0.09, 0.28)	**1.71×10^{-4}**	0.05; (-0.03, 0.14)	0.198	0.13; (0.05, 0.20)	**1.28×10^{-3}**
	Body hair growth	FVC	0.14; (0.04, 0.23)	**4.27×10^{-3}**	0.06; (-0.02, 0.13)	0.140	0.08; (0.01, 0.15)	**0.017**
	Menarche	FEV_1	0.21; (0.11, 0.30)	**1.88×10^{-5}**	0.12; (0.04, 0.20)	**$5.15\text{x}10^{-3}$**	0.09; (0.01, 0.17)	**0.028**
	Body hair growth	FEV_1	0.13; (0.03, 0.23)	**8.01×10^{-3}**	0.06; (-0.02, 0.13)	0.122	0.07; (0.01, 0.14)	**0.043**
ALSPAC	Menarche	FVC	0.25; (0.21, 0.30)	**$<10^{-31}$**	0.05; (0.00, 0.10)	0.054	0.21; (0.17, 0.24)	**$<10^{-31}$**
	Body hair growth*	FVC	0.16; (0.12, 0.20)	**5.99×10^{-14}**	0.02; (-0.01, 0.06)	0.252	0.13; (0.11, 0.16)	**$<10^{-31}$**
	Menarche	FEV_1	0.25; (0.21, 0.29)	**$<10^{-31}$**	0.05; (0.00, 0.10)	0.066	0.20; (0.17, 0.24)	**$<10^{-31}$**
	Body hair growth	FEV_1	0.15; (0.11, 0.19)	**1.67×10^{-12}**	0.02; (-0.02, 0.06)	0.570	0.13; (0.11, 0.17)	**$<10^{-31}$**

Note: [#] Est: Regression coefficient estimates. The unit for all the regression coefficients is liter/year representing expected lung function change for one year increase in pubertal age. CI: Confidence Interval.

*Age at body hair growth is identified by age at attainment of Tanner stage>2 in ALSAPC cohort.

TABLE 2B Statistically significant effects of ages of pubertal events onset on lung function at age 26 years through height growth and lung function at age 18 years in *males* in IOW, further tested in the replication cohort, ALSPAC. For the IOW, only statistically significant results are included in the table

Cohort	Age of onset of Pubertal events	Lung function	Total effect Est. (L)#; 95%CI	p-value	Direct effect Est. (L); 95% CI	p-value	Indirect effect Est.(L); 95% CI	p-value
IOW	Body hair growth	FVC	0.15; (0.04, 0.25)	**5.77×10^{-3}**	0.07; (-0.01, 0.15)	0.078	0.08; (0.01, 0.15)	**0.047**
	Growth spurt	FVC	0.13; (0.02, 0.24)	**0.017**	0.04; (-0.04, 0.12)	0.282	0.09; (0.01, 0.17)	**0.034**
	Facial hair growth	FVC	0.18; (0.08, 0.28)	**5.35×10^{-4}**	0.09; (0.01, 0.16)	**0.026**	0.09; (0.02, 0.16)	**0.014**
ALSPAC	Body hair growth*	FVC	0.07; (0.02, 0.12)	**0.006**	0.03; (-0.02, 0.08)	0.219	0.04; (0.01, 0.07)	**0.003**

Note: # Est: Regression coefficient estimates. The unit for all the regression coefficients is liter/year representing expected lung function change for one year increase in pubertal age.

* In the IOW cohort, mediation effects were observed for FVC only. Thus, in the replication cohort ALSPAC, only FVC was evaluated. The ages of growth spurt and facial hair growth were not available in ALSPAC. Age at body hair growth is identified by age at attainment of Tanner stage>2 in ALSAPC cohort.

Discussion

Using IOW as the discovery cohort and ALSPAC as the replication cohort, this study has demonstrated using path analysis that height growth during adolescence in both sexes mediates the association of age at pubertal onset with lung function parameters FVC in adults. For FEV_1, the same pattern as for FVC was observed in females, but not in males.

With respect to the total effects (direct effects plus indirect effects), for females, our results support findings from previous studies that early age at menarche is associated with reduced FVC and FEV_1 in young adults [12, 13, 15]. In addition, this study extends these previous observations by demonstrating that the majority of the total effects of age at onset of pubertal events on adult lung function are indirect, via the effect of age at puberty on height growth. The dominance of indirect effects of age at puberty in females highlights the importance of adolescence growth on lung function development. The indirect effects of age at menarche explained 72% and 84% of the total effects in the IOW and ALSPAC cohorts, respectively, and thus a much larger sample size was required to detect the remaining small amount of direct effects. The contribution of indirect effects in this study is higher than those observed in a recent study, where 40% of the total effects of an early age at menarche on FVC at ~53 years was explained by indirect effects via adult-attained height [30]. The discrepancy might have been due to the use of different mediators related to height as well as the age

of FVC measurement. In our study, the mediator height growth took the baseline height into account rather than one time point height, and FVC was measured at a much younger age, 26 years, an age with FVC still close to its maximum value while at age ~53 years, significant lung function decline was expected.

Putting together findings in females and males, indirect effects of age of puberty on FEV_1 were shown in females but not males. These different relationships might be attributed to different pattern of lung function development during adolescence in both sexes [17]. Females have a shorter duration of lung function growth during adolescence and attain maximum lung volumes at an earlier age after puberty [15, 31]. At age 18, lung volume growth has almost reached maximum values in females but continues to increase in males until around 20 years [31]. Although further studies are warranted, the findings of both this study and previous studies imply that development of FVC and FEV_1 in adolescence in females are likely follow similar patterns [32, 33], whilst in males growth of FVC and FEV_1 during adolescence may follow different patterns.

To our knowledge, this is the first study that has examined whether and to what extent height growth during adolescence mediates the effect of age of pubertal onset on lung function longitudinally in both females and males. Our study offers an insight to explore possible "causal pathways" from pubertal onset to lung function in young adulthood [34] and an opportunity to better understand the role of height growth in the connection between pubertal events and lung function. In addition to height growth, peak velocity of height growth, although not available in the IOW cohort, may be another mediator as previously observed in the ALSPAC cohort [15].

This study has some limitations. Age at pubertal events were determined retrospectively based on responses to questionnaires collected at age 18 years in IOW and recall bias might have affected their reports. However, internal consistency of the age of onset of the different pubertal events in the IOW has previously been demonstrated, implying the validity of these variables [16]. In the ALSPAC cohort, age of onset of some pubertal events were measured by tracking pubertal growth using Tanner stages at follow-ups from 9 to 17 years [35, 36], and misclassification of pubertal stages

might occur. Finally, in the path analysis, we might have overlooked other unknown confounders which might impact the mediation effects of height growth in adolescence on the association of age at puberty with lung function in early adulthood.

Conclusions

Our study demonstrated that height growth during adolescence in females mediated the association of age of pubertal onset with FVC and FEV_1 in late adolescence and young adulthood. In males, such mediation effects were identified for FVC but not FEV_1, implying dysanaptic growth of FVC and FEV_1 during adolescence between the two sexes. The findings indicate the needs to promote height growth in adolescence through interventions such as better nutrition and appropriate physical activities to improve lung function in adulthood and reduce future risk of COPD.

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Conflict of interest: All authors are nothing to disclose.

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Pubertal onset with adulthood lung function mediated by height growth in adolescence

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Supplementary materials

Contents

S. 1. Sample sizes at each follow-up for the study variables.

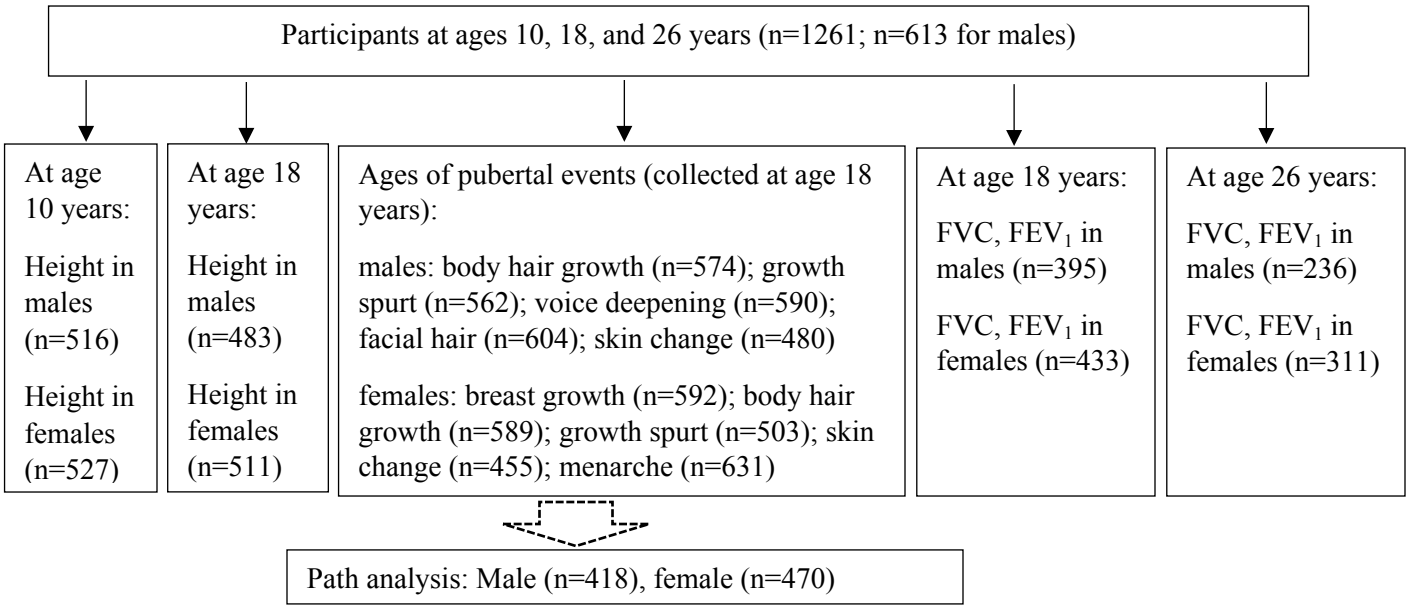

FIGURE S1 Sample sizes at each follow-up for the study variables.

S. 2. Identification of pubertal events and lung function parameters to be included in path analyses (Figure 1 in the main text).

To identify pubertal events and lung function parameters to be included in path analyses, we examined the association of ages at pubertal events onset with height growth during adolescence as well as their associations with three lung function parameters, FVC, FEV_1 at ages 18 and 26, using data in the IOW cohort. Statistical significance is set at 0.05.

For each gender, ages at five pubertal events were tested (Table S1) and our data showed statistically significant positive associations between ages of pubertal events and height growth for all the pubertal events in both genders. That is, the later the age of puberty, the larger the height growth between ages 10 and 18 years.

TABLE S1 The association of age of pubertal events and height growth from ages 10 to 18 years in the IOW cohort. Potential confounders adjusted in the model including asthma status at age 10 years, height

at age 10 years, BMI at age 10 years, SES at age 10 years, birth weight status, maternal smoking during pregnancy (Figure 1 in the main text)

Female			Male		
Pubertal events	Coeff. Estimate[#]	p-value	Pubertal events	Coeff. Estimate[#]	p-value
Breast growth	0.007	$\mathbf{7.57\times10^{-12}}$	Body hair growth	0.005	$\mathbf{2.13\times10^{-4}}$
Body hair growth	0.006	$\mathbf{2.25\times10^{-6}}$	Growth spurt	0.004	$\mathbf{1.34\times10^{-4}}$
Growth spurt	0.007	$\mathbf{8.79\times10^{-9}}$	Voice deepening	0.005	$\mathbf{1.04\times10^{-4}}$
Skin changes	0.005	$\mathbf{1.50\times10^{-4}}$	Facial hair	0.004	$\mathbf{8.37\times10^{-3}}$
Menarche	0.011	$\mathbf{1.34\times10^{-17}}$	Skin changes	0.003	$\mathbf{4.06\times10^{-2}}$

[#]: Coeff. Estimate: Regression coefficient estimates.

We next examined ages of these pubertal events on their associations with lung function parameters at ages 18 and 26 years in the IOW cohort.

In females, for lung function parameters measured at age 18 years, the associations of age at menarche with FVC and FEV_1 were statistically significant (Table S2). For age 26 years lung function parameters, ages of body hair growth and menarche onset showed statistically significant associations with FVC and FEV_1 (Table S3). For males, ages of body hair growth, growth spurt, voice deepening, and appearance of facial hair growth were associated with FVC at age 26 years. No other statistically significant associations were identified at these two ages.

Lung function parameters at ages 18 or 26 years and pubertal events showing statistically significant associations were included in path analyses. Specifically, FVC, FEV_1ages at body hair growth and menarche for females, and ages at body hair growth, growth spurt, voice deepening, and appearance of facial hair growth for males were included in subsequent path analyses (Tables S2 and S3).

TABLE S2 Estimated regression coefficients for the association of age of pubertal events onset with lung function at age 18 years in the IOW cohort. Potential confounders adjusted in the model including Asthma status at age 10 years, height at age 10 years, BMI at age 10 years, SES at age 10 years, birth weight status, maternal smoking during pregnancy (Figure 1 in the main text)

Female				Male		
Lung function	Pubertal events	Coeff. Estimate[#]	p-value	Pubertal events	Coeff. Estimate[#]	p-value
FVC	Breast growth	0.000	0.998	Body hair growth	0.017	0.546
	Body hair growth	0.030	0.096	Growth spurt	0.013	0.607
	Growth spurt	0.017	0.327	Voice deepening	0.016	0.601
	Skin changes	0.021	0.280	Facial hair growth	0.054	0.096
	Menarche	0.046	**0.014**	Skin changes	0.025	0.411
FEV_1	Breast growth	0.007	0.605	Body hair growth	0.020	0.402
	Body hair growth	0.022	0.152	Growth spurt	0.013	0.535
	Growth spurt	0.018	0.225	Voice deepening	0.018	0.471
	Skin changes	0.008	0.611	Facial hair growth	0.030	0.285
	Menarche	0.033	**0.040**	Skin changes	0.007	0.782

[#]: Coeff. Estimate: Regression coefficient estimates, and the unit presented in litres(L).

TABLE S3 Estimated regression coefficients for the association of age of pubertal events with lung function at age 26 years in the IOW cohort. Potential confounders adjusted in the model including Asthma status at age 10 years, height at age 10 years, BMI at age 10 years, SES at age 10 years, birth weight status, maternal smoking during pregnancy, and smoking at age 18 years. (Figure 1 in the main text)

Female				Male		
Lung function	Pubertal events	Coeff. Estimate[#]	p value	Pubertal events	Coeff. Estimate[#]	p value
FVC	Breast growth	0.042	0.056	**Body hair growth**	0.099	**0.020**
	Body hair growth	0.055	**0.022**	**Growth spurt**	0.086	**0.021**
	Growth spurt	0.038	0.070	**Voice deepening**	0.115	**0.016**
	Skin changes	0.035	0.161	**Facial hair growth**	0.111	**0.029**
	Menarche	0.077	**0.001**	Skin changes	0.052	0.299
FEV_1	Breast growth	0.020	0.249	Body hair growth	0.052	0.171
	Body hair growth	0.044	**0.019**	Growth spurt	0.041	0.223
	Growth spurt	0.025	0.121	Voice deepening	0.055	0.205
	Skin changes	0.032	0.103	Facial hair growth	0.031	0.492
	Menarche	0.067	**0.000**	Skin changes	0.035	0.447

[#]: Coeff. Estimate: Regression coefficient estimates, and the unit presented in litres(L).

S. 3. Results on the mediation effects of height growth on the associations of age at pubertal events onset with lung function parameters in the IOW cohort, along with testing results in the ALSPAC cohort.

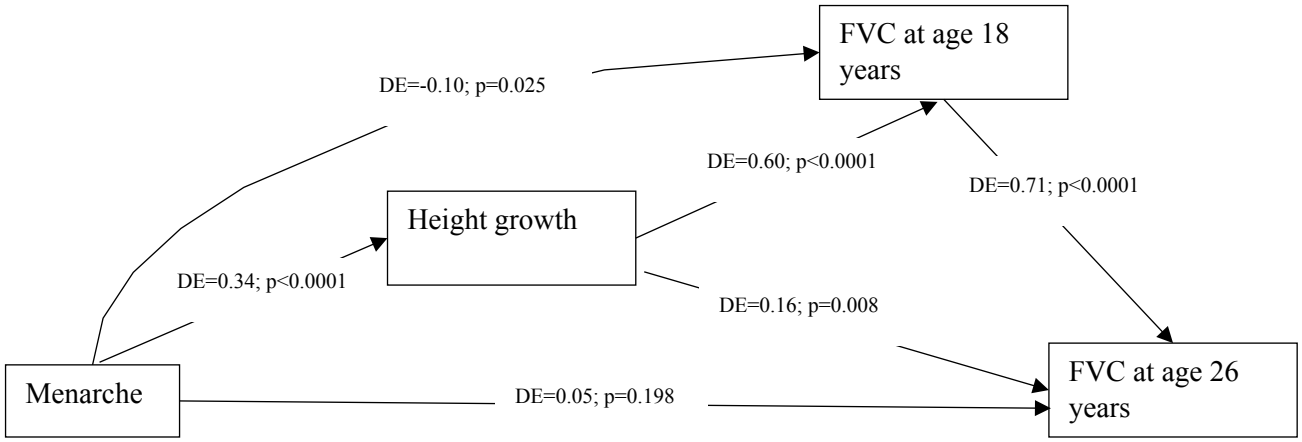

FIGURE S2 Estimated direct effects of each path (IOW), age at menarche and lung function parameter FVC.

The Principe of path (or mediation) analysis is to analyze that an initial variable X may influence an outcome variable Y through a mediating variable M or multiple mediators, such as M1, M2, et.al.
In our study, the X is age of onset of puberty; Y is lung function parameters at age 26 years; and M1 is height growth and M2 is lung function at age 18 years.

Direct effect assesses the effect of one variable (independent variable or exogenous variable) to another variable (dependent variable or endogenous variable) evaluated using a regression model. For example, the direct effect of age at menarche on FVC at age 26 is assessed by regressing FVC at age 26 years on age at menarche and the regression coefficient represents the direct effect.
Indirect effect is the effect of one variable on another variable through one or more variables in between (i.e., mediators). For instance, age of menarche indirectly affects FVC at age 26 through height growth and/or FVC at age 18 years.

Conceptually, a total effect is the sum of direct and indirect effects. In our study, the total effect of age at menarche on FVC at age 26 years is the sum of all the direct and indirect effects explained above.
We give an example to interpret indirect effect. The indirect coefficient (IEC) of 0.13 for age at menarche means that, with other factors kept constant, one year delay in the onset of menarche was associated with a 0.13 Liter increase in FVC at age 26 years. One of such indirect paths was later menarche → larger height growth → higher lung function FVC at age 18 years → higher lung function FVC at age 26 years (the estimated effect was 0.34*0.60*0.71=0.14). The second indirect path is later menarche →larger height growth → higher lung function FVC at age 26 years (the estimated effect was 0.34*0.16=0.054), and the third path is through FVC at 18 years (-0.10*0.71=-0.071). Adding all portions of indirect effects up, we have IEC= -0.10*0.71+0.34*0.60*0.71+0.34*0.16=0.13 for age at menarche.

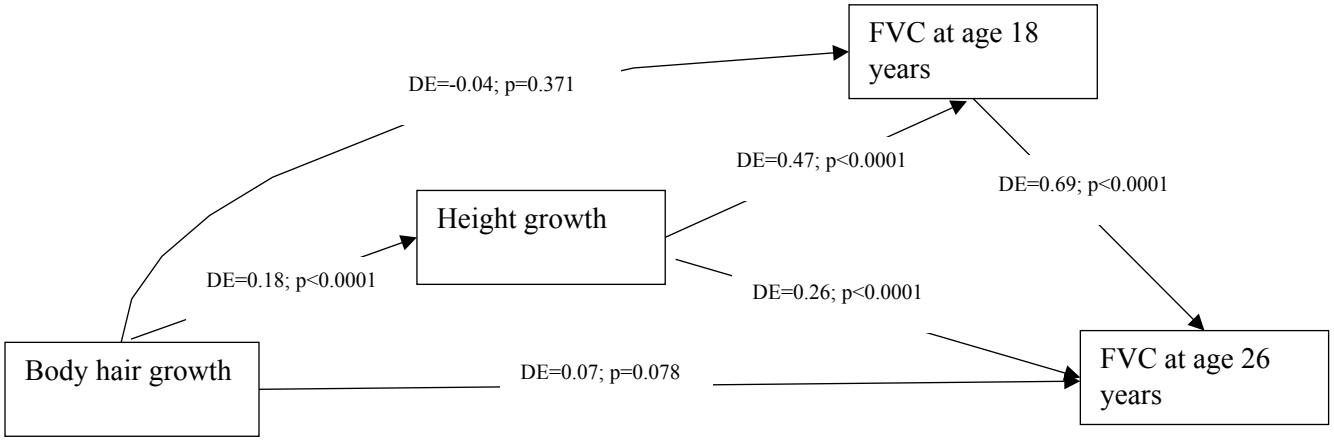

FIGURE S3 Estimated direct effects of each path (IOW), age at body hair growth and lung function parameter FVC in males.

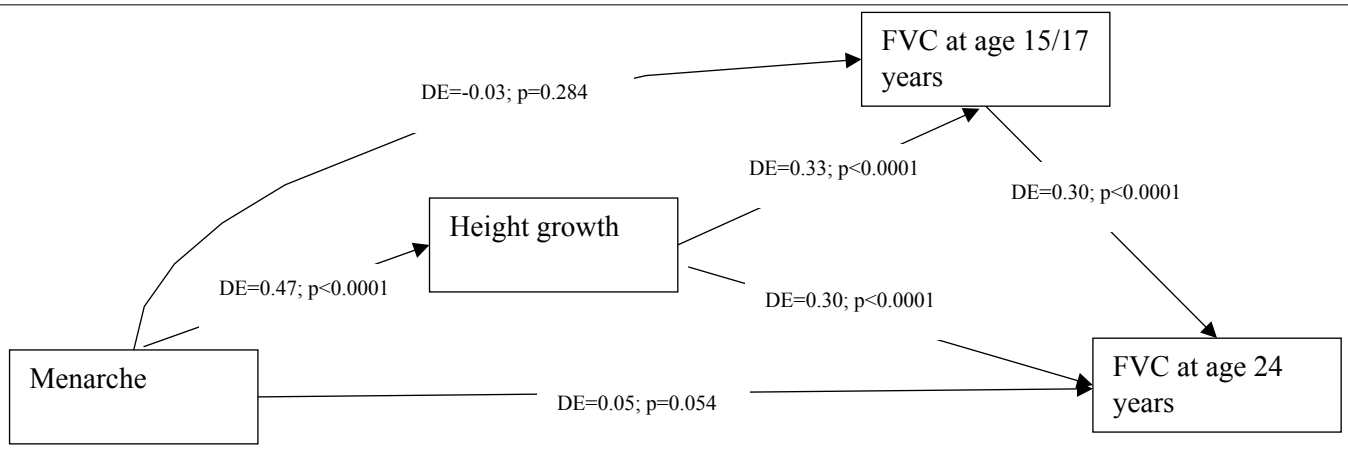

FIGURE S4 Estimated direct effects of each path (ALSPAC), age at menarche and lung function parameter FVC in females.

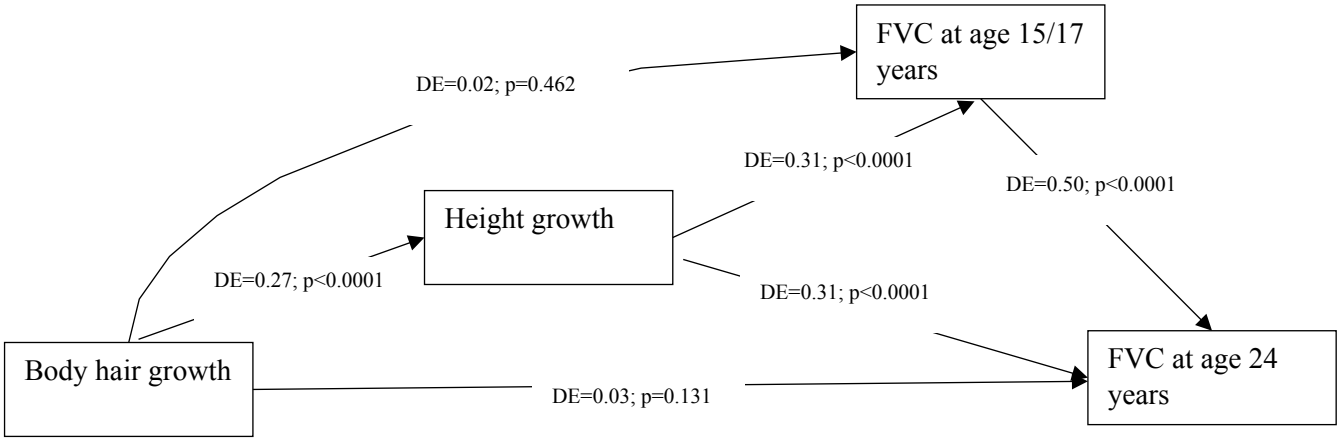

FIGURE S5 Estimated direct effects of each path (ALSPAC), age at body hair growth and lung function parameter FVC in females.

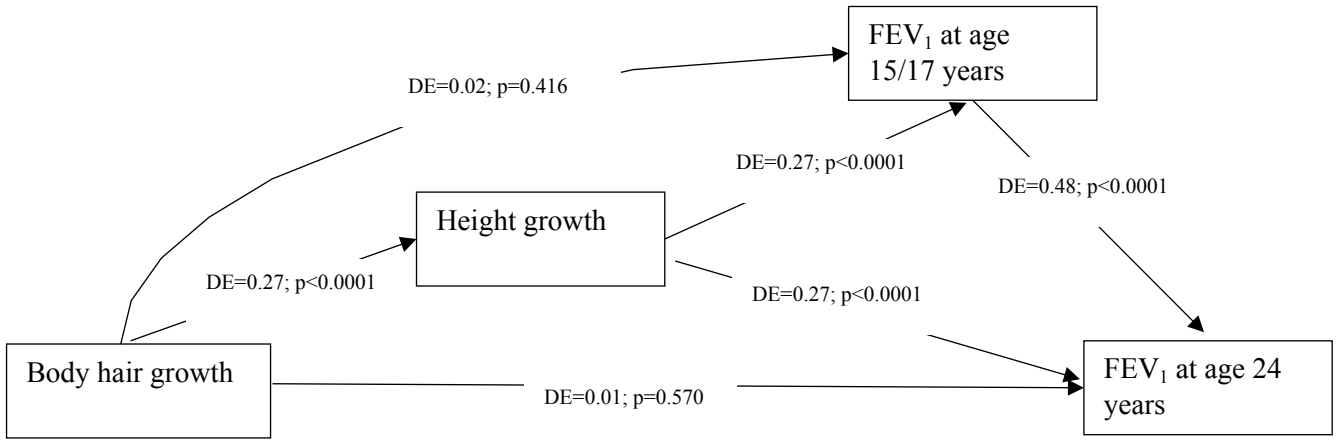

FIGURE S6 Estimated direct effects of each path (ALSPAC), age at body hair growth and lung function parameter FEV_1 in females.