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

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O.M. and J.H. conceived and designed the study. O.M. planned, designed and conducted the statistical analyses, and drafted the manuscript. O.M., R.G., K.T., C.M., J.G.A, J.W.H., A.C., D.J., J.S. and J.H. contributed to the interpretation of the results, critically reviewed the manuscript, and approved the final version.

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**AT A GLANCE COMMENTARY**

**Scientific Knowledge on the Subject:** Low lung function at the physiological plateau in early adulthood is associated with chronic obstructive pulmonary disease in later life. Lung development during childhood and adolescence influences maximally attained lung function in early adulthood. Puberty is a crucial phase in this process, during which a series of programmed biological changes occur that may influence lung function. Height, a key developmental factor during puberty, is strongly correlated with lung function, but little is known about the influence of the characteristics of the pubertal height growth on subsequent lung function.

**What This Study Adds to the Field:** This population based, birth cohort study with repeat measurements of anthropometry and lung function from childhood to early adulthood shows that later onset and higher velocity of pubertal growth are associated with higher maximally attained lung function at age 24 years in both sexes, with a greater magnitude in males than females.

At a glance commentary word count: 152 (Max. 200)

## ABSTRACT

**Rationale:** Puberty may influence lung function, but the precise role of pubertal height growth in lung development is unclear.

**Objectives:** To examine associations of timing of puberty and peak velocity of pubertal height growth with lung function in adolescence and early-adulthood.

**Methods:** Longitudinal analyses of repeat height measurements from age 5-20 years for a British birth cohort with 4,772 males and 4,849 females were conducted to characterise height growth trajectories, and derive pubertal age and peak height velocity using the validated SuperImposition by Translation and Rotation (SITAR) model. Association of these estimates with pre-bronchodilator and post-bronchodilator spirometry measures: $FEV_1$; FVC; $FEV_1$/FVC; $FEF_{25-75}$ at age 15 and 24 years were investigated using multivariable regression models adjusted for lung function at age 8 years, height and age at time of outcome measurements, and potential confounders.

**Measurements and Main Results:** Later pubertal age and greater peak velocity were associated with higher $FEV_1$ and FVC at 24 years in both sexes. A 1-year advanced pubertal age was associated with a 263 ml higher FVC (95% confidence interval: 167, 360) for males (n=567), 100 ml (50, 150) for females (n=990). A 1-cm/year increase in peak velocity was associated with 145 ml (56, 234) and 50 ml (2, 99) increase in FVC for males and females respectively. No associations were found with $FEV_1$/FVC.

**Conclusions:** Later onset and greater peak velocity of height growth in puberty are associated with increased $FEV_1$ and FVC in young adults but there was no evidence of dysanapsis of pubertal lung growth.

**Abstract word count:** 250 (Max. 250)

**Keywords:**

ALSPAC; SITAR; Pubertal age; Velocity of pubertal height growth; Maximal lung function.

## INTRODUCTION

Pubertal growth is a pivotal phase in the life course whose characteristics can influence adulthood health outcomes including type 2 diabetes (1), cardiovascular mortality (2), ovarian (3) and testicular (4) cancers. Understanding the role of pubertal growth in subsequent health conditions may provide insight into heterogeneous pathophysiology of related diseases and explain growth-related differences in their associated risks (5-7). Timing of pubertal growth has shown a secular trend towards earlier ages over years (8), which is related to childhood life-style and social factors, e.g. diet, obesity, deprivation and psychological stress, as well as environmental exposures including endocrine disruptors found in several household products (9, 10).

Previous studies investigating association of puberty with later health outcomes have largely relied on deriving pubertal age using recalled sexual development such as age at first menstrual bleeding (11-14), self-reported attainment of breast (15) and pubic hair (16) Tanner stages for females; and self-reported attainment of testis , pubic hair Tanner stages (17) and voice deepening (18) for males. Although these methods have some validity, their reliability may depend on characteristics of the study population including age at recall and socioeconomic factors such as educational attainment and social class (19). Moreover, methods of tracking pubertal growth using Tanner stages may not reveal precise pubertal timing since sexual characteristics are assessed at specific time points and the attained Tanner stage is reported, with no information on exact age at attainment. In addition, subjective assessments, particularly around the transition to a higher Tanner stage, may lead to misclassification problems. As a result, these methods may bias estimates of the effects of

pubertal age. The velocity (speed) of pubertal growth is another parameter whose role in relevant health outcomes, e.g. adulthood lung function, remains incompletely understood.

Age at first menstrual bleeding has been associated with respiratory health conditions in women (14, 20), including low lung function, a major predictor of disability and mortality in adults (21). Impairments of lung function, either obstructive, defined as low ratio of forced expiratory volume in one second ($FEV_1$) to forced vital capacity (FVC), or restrictive, defined as low FVC, are major causes of disability and death worldwide (22-24). There has been a growing interest in identifying childhood risk factors associated with impaired lung function in adulthood, particularly those related to pubertal development. For instance, earlier age at menarche has been associated with reduced FVC in women with no effect found on $FEV_1$/FVC (14). These findings were confirmed by a Mendelian randomization study of 46,944 adult women and 3,025 adolescent girls investigating the causal effect of age at menarche on lung function, using 122 genetic variants as instrumental variables (20). Of note, consistent findings were shown in men in whom the same genetic variants were used as instrumental variables for sexual development (20). This may suggest a role for pubertal age in general rather than for menarche specifically.

Pubertal height growth has been used as an effective marker for pubertal development (25). Height is an objective measure that can be easily obtained, and of particular importance when respiratory health is considered because it is related to lung volumes (26). Through identification of the individual height growth trajectories, we can examine association of age as well as velocity of pubertal height growth with lung function in both males and females; and reveal gender growth-related differences in lung development.

In this study we used a validated SuperImposition by Translation and Rotation (SITAR) model (27) to characterise individual height growth from age 5-20 years and investigate the associations of pubertal age and height velocity with lung function in adolescent and young adult males and females.

## METHODS

### Study design, setting and population

We studied participants of the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based birth cohort. The study protocol was described previously (28), and a detailed description is reported in the online data supplement. Briefly, 46,944 pregnant women resident in Avon, UK with expected delivery dates between April 1, 1991 and December 31, 1992 were recruited, and their live-born children were followed prospectively. There was a total of 46,944 fetuses, resulting in 46,944 live births and 46,944 children who were alive at 1 year of age. Participant flow is shown in Figure 1. The study was approved by the ALSPAC Ethics and Law Committee and local research ethics committees.

### Height growth in puberty

Longitudinal measurements of height were mainly obtained from direct measurement in annual research clinics from age 7 to 13 years and at 15, 17 and 24 years. These were supplemented with maternal and self-reported measures throughout the duration of the study. Standing height was measured to the last complete millilitre by trained clinic staff. For characterising individual height growth trajectories, we considered measurements between the ages of 5 to 20 years for those participants who had at least one height measured after 9

years old ($n = 9{,}621$, excluding quadruples, triples and one random child from each alive twin).

Height growth curves by sex were fitted using the SuperImposition by Translation and Rotation (SITAR) model, a validated non-linear mixed effects model (27). The SITAR model explains most of the population heterogeneity in pubertal height growth through characterising variability in pubertal age, measured by age at peak height velocity (APV) and magnitude of peak height velocity (PV), see Figure 2. Additional detail on the SITAR model is provided in the online data supplement. Median, interquartile range (IQR), correlation of APV and PV, and standard deviations and correlations of the SITAR model's random effect parameters were obtained to describe the height growth in puberty.

**Lung function**

We performed spirometry according to standards of the ATS/ERS criteria (29, 30) in research clinics at ages 8, 15 and 24 years. Lung function at 15 and 24 years were reported before and 15 minutes after receiving 400 μg of salbutamol administered by metered aerosol through a spacer (31, 32). The highest measurement of each lung function variable ($FEV_1$, FVC, $FEV_1$/FVC, and forced expiratory flow between 25% and 75% ($FEF_{25-75}$)) amongst the best three technically acceptable flow-volume curves was used for analyses. Post-bronchodilator (post-BD) lung function variables at age 15 and 24 years were used as the primary outcomes, which were summarized using the median and IQR. Missing lung function data were examined to assess whether they were plausibly missing at random, details are reported in the online data supplement.

**Statistical analysis**

The associations of APV and 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. 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. Detailed description of statistical analyses is reported in the online data supplement.

Sex differences among characteristics of interest were examined using $\chi^2$ and Mann Whitney tests for categorical and continuous factors respectively. Associations of potential confounders with lung function outcomes were examined using multiple linear regression models. 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 ($\geq 1$ 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.

Several secondary analyses were performed to address the robustness of our findings: (1) pre-bronchodilator (pre-BD) measurements were used as lung function outcomes; (2) secondary sexual characteristics such as age at menarche for females and pubic hair development for males were used as measures of pubertal development; (3) post-BD lung

function excluding the lowest and highest 1% of measurements were used to examine the sensitivity to extreme spirometry values; (4) we performed $k$-means cluster analysis to identify groups of subjects with similar pubertal growth in terms of APV and PV. The associations of clusters of identified pubertal patterns with lung function were then examined to assess pattern-specific differential risks; (5) a sensitivity analysis was performed to investigate the association between lung function at 8 years old and pubertal growth to assess potential reverse causation (i.e. that lung function in childhood was affecting puberty); (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. Details of the secondary analyses are provided in online data supplement. All analyses were adjusted for lung function at age 8 years, height and age at time of lung function measurements. The analyses were conducted using R software (33).

## RESULTS

### Characteristics of the study population

Among 9,621 subjects with at least one observation of height measured after age 9 years (the study population), 4,849 (50.4%) were female. Table 1 reports characteristics of the study population by sex. A similar proportion of male and female subjects had an asthmatic or allergic mother (47.4% in males vs 46.5% in females), were exposed to maternal smoking during pregnancy (23.3% vs 22.3%), had at least one sibling (53.8% vs 54.5%), and low birth weight (4.3% vs 4.7%). More male subjects were born preterm (5.9% vs 4.7%, $P = 0.01$), reported positive doctor-diagnosed asthma ever by 14 years of age (36.4% vs 30.2%, $P = 2 \times 10^{-7}$) compared with female subjects. Whereas female subjects were more exposed to

maternal anxiety during pregnancy (32.6% vs 29.8%, $P = 0.009$), and had higher proportion of smokers by age 14 years (31% vs 18.6%, $P = 2 \times 10^{-16}$) compared with male subjects. Male subjects had higher baseline $FEV_1$ and FVC measurements at 8 years of age ($P = 2 \times 10^{-16}$), were taller and attended earlier, in relation to their birth date, at the 15-year visit clinic (largest $P = 7 \times 10^{-4}$), and taller and attended later, in relation to their birth date, at the 24-year visit clinic (largest $P = 0.001$) compared with female subjects.

**Longitudinal analysis of pubertal height growth**

A total of 33,367 and 33,783 measurements were included in the analysis for 4,772 males (median 8 measurements, IQR 4 to 9 and range 1 to 20), and 4,849 females (median 8, IQR 5 to 9 and range 1 to 18) respectively. The SITAR model explained 96.2% and 96.6% of the height growth variation in males and females with residual standard deviation 13 and 12 millimetre respectively (Table E2). The median (IQR) APV was 13.5 (13.0 to 13.9) for males and 11.7 (11.2 to 12.1) years for females and the median (IQR) PV was 9.9 (9.3 to 10.5) and 8.0 (7.5 to 8.5) cm/year respectively (Figure 2 and Table E2). The correlations between APV and self-reported pubertal staging, i.e. age at menarche and age at advanced pubic hair Tanner stage (>2), were 0.71 and 0.26 for females and males respectively. In both sexes, growth curves were steeper for those with an early puberty and shallower for individuals who attained puberty later, correlation (APV, PV) = -0.70 and -0.62 for males and females respectively. The estimated subject-specific parameters confirmed these relationships (Table E3). There were positive correlations, 0.29 and 0.20 for males and females respectively, between velocity and size (magnitude of height). These suggest that children with relatively higher PV tend to remain on their height trajectory achieving above average adulthood height (Table E3).

**Lung function outcomes**

Structures of missingness of lung function data at ages 8, 15 and 24 years are presented in Figure E1. Table E4 shows that parity, maternal smoking during pregnancy, exposure to smoke from birth to age 8 years, ever doctor-diagnosed asthma by age 14 years and smoking by age 23 years were related to chance of missing the next lung function data, but the current lung function measurements were not. This implies that data are likely to be missing at random and that our analyses, considering all variables related to missingness, should be unbiased.

Table 2 summarizes the distribution of lung function outcomes at age 15 and 24 years in the study population and restricted to subjects with complete data on confounding and control variables by sex. At age 24 years, the median FVC was 5.50 litres (IQR: 5.00 to 6.06) and 3.89 litres (IQR: 3.53 to 4.24) and the median $FEV_1$ was 4.61 (IQR: 4.19 to 5.04) and 3.36 (IQR: 3.06 to 3.66) for male and female subjects respectively. Male subjects had higher spirometry measurements (FEV1, FVC and FEF25-75) at both ages compared with female subjects. These measurements were similar when data was restricted to subjects with complete data on confounders and control variables.

**Associations of pubertal height growth with lung function**

At age 24 years, a 1-year increase in APV was associated with 263 ml (95% CI: 180 to 346, $P = 1 \times 10^{-9}$) increase in $FEV_1$ in males and 100 ml (95% CI: 59 to 141, $P = 1 \times 10^{-6}$) in females. Similar findings were obtained for FVC (263 ml, 95% CI: 167 to 360, $P = 1 \times 10^{-7}$ in males; 100 ml, 95% CI: 50 to 150, $P = 8 \times 10^{-5}$ in females) and $FEF_{25\text{-}75}$ in males (270 ml/s, 95% CI: 114 to 425, $P = 7 \times 10^{-4}$), see Figure 3 and Table E6. In contrast, at age 15

years the APV in males was inversely associated with lung function measurements: $FEV_1$ (-100 ml, 95% CI: -150 to -50, $P = 8 \times 10^{-5}$); FVC (-103 ml, 95% CI: -158 to -49, $P = 2 \times 10^{-4}$); $FEF_{25-75}$ (-168 ml/s, 95% CI: -250 to -86, $P = 6 \times 10^{-5}$). There was no evidence of association between pubertal age and lung function at 15 years in females.

At age 24 years, a 1cm/year increase in PV was associated with 161 ml (95% CI: 85 to 237, $P = 4 \times 10^{-5}$) increase in $FEV_1$ in males, 46 ml (95% CI: 6 to 86, $P = 0.025$) in females (Figure 4, Table E7). Similarly for FVC, a 1cm/year increase in PV was associated with 145 ml (95% CI: 56 to 234, $P = 0.001$) increase in males and 50 ml (95% CI: 2 to 99, $P = 0.043$) in females. Evidence of association with $FEF_{25-75}$ was only found in males (163 ml/s per 1cm/year increase in PV, 95% CI: 17 to 308, $P = 0.029$). At age 15 years, lung function measurements, i.e. $FEV_1$, FVC, $FEF_{25-75}$, showed the same direction of association with PV as at age 24 years in males (largest $P = 9 \times 10^{-5}$), with no or little evidence of association in females (lowest $P = 0.034$). For both genders, results show that the PV is more important than APV as a predictor for adolescence lung function, whereas for adulthood lung function the APV plays the dominant role, see Tables E6 and E7 and 'Statistical analyses' section in the online data supplement for more details.

Results obtained from secondary analyses confirmed the findings of the study (Table 3, E8-E11 and Figures E5-E6 in the online data supplement).

**Associations of pubertal height growth with asthma symptoms and wheezing**

Advanced pubertal age and increased magnitude of peak height velocity were associated with 28% (95% CI: 13 to 41) and 21% (95% CI: 6 to 34) lower risk of asthma symptoms respectively in adolescence, and 21% (95% CI: 6 to 34) and 22% (95% CI: 7 to 34) lower risk

of wheezing in early adulthood for females. Whereas for males, there was some evidence that higher peak velocity is associated with 19% (95% CI: 2 to 34) lower risk of asthma symptoms in adolescence, see Table 4.

## DISCUSSION

### Main findings

This large, population-based birth cohort study shows that both pubertal age and peak height velocity, estimated from individual-level longitudinal height growth curves, are associated with lung function in early adult life, around the time of maximal lung function attainment. In both sexes, we found an association of later pubertal age and rapid pubertal growth on increased FVC with no evidence of an effect on large airway obstruction ($FEV_1$/FVC) suggesting that the effect of pubertal growth is manifested by increase of both $FEV_1$ and FVC with no evidence of dysanaptic growth occurring during pubertal development. In contrast in adolescent males, we showed that later pubertal age was associated with decreased lung function, which may indicate a lag between height growth and lung function maturation during puberty. Additionally, we showed that rapid pubertal growth was associated with increased FVC, $FEV_1$ and $FEF_{25-75}$ in males in adolescence and early adulthood, with less evidence of an effect in females.

### Findings in the context of the literature

The findings of this study support previous evidence suggesting an increase in FVC of 123 ml ($P = 0.01$) in women associated with one year later age at menarche, but no association with $FEV_1$/FVC (14). Our finding in adult males, showing a similar association with FVC, confirms

the Mendelian randomisation findings suggesting effects of pubertal age in general rather than menarche specifically (20).

The inverse association of APV with FVC at 15 years in males is intriguing and contrast with the relationships in females. Lung volume increases during childhood are generally linear up until puberty and related largely to height growth in both sexes (34). However, during the pubertal growth spurt, there is uncoupling of growth in chest wall dimensions with height increases, such that thoracic growth lags behind leg and height growth (35). Lung volumes continue to increase after height growth ceases but there is evidence that the pattern differs between males and females; the latter have a shorter duration of lung development and lung volume increases have completed by the occurrence of menarche (36). In contrast, lung volume increases in males continue throughout puberty and beyond the point at which final adult height is reached. We interpret the differential relationship seen at 15 years in this study in the context of most females having completed menarche by this age but a sizeable proportion of males being in mid-puberty. Coupled with the lag between height and thoracic development growth, we believe this observation is most likely explained by the timing of lung function measurement in relation to pubertal status.

Although pubertal growth has clearly an important influence on lung function, the plateau phase of lung function development usually occurs in early to mid-twenties (21). The association of greater magnitude of PV with increased lung function at 15 and 24 years could possibly be explained by rapid pubertal growth influencing lung function directly as well as leaving a longer interval for post-pubertal lung development prior to achieving plateau values. It is conceivable that our findings reflect the inverse relationship between the

pubertal age and magnitude of peak height velocity for both sexes. This confirms the clinical observation that pubertal timing and velocity are inversely correlated (37).

**Strengths and limitations**

This study offers insights into the roles of pubertal height growth in maximal lung function which can shape the respiratory health in late adulthood. Our study utilised repeated height measurements, covering span of childhood through early adulthood, to which we applied well validated mixed-effects model (SITAR) for characterising growth in puberty. As a result, pubertal age and peak height velocity were derived and explained more than 96% of variability in pubertal height growth among subjects. This approach avoided potential problems of most traditional methods used for investigating growth in puberty such as the Tanner stages, e.g. misclassifications of pubertal stages. Our findings highlight potential implications of the secular trend shifting to earlier attainment of puberty over years (8). We addressed the associations of height growth with different lung function parameters including $FEV_1$, FVC and $FEF_{25-75}$. We minimized potential reverse causation by adjusting results for lung function at age 8 years. Another strength is that the study accounts for a wide range of potential confounders with detailed information provided by the ALSPAC cohort.

There are some limitations to our study design and findings. We had no information on hormone levels, the gold standard to measure puberty. Therefore, the influences of hormones could not be addressed. However, our secondary analyses showed consistency in results using other proxy measures, including timing of appearance of secondary sexual characteristics. We supplemented height measurements taken at the research visit clinics with some self-reported heights. The complex physiological changes that occur in puberty

challenge the identification of precise mechanisms underlying our findings on pubertal age and peak height velocity suggesting a need for further research to investigate them. Our study population is liable to loss to follow up that related to socioeconomic factors. However, there is no evidence that its potential bias might affect the association of puberty with lung function.

**Conclusions**

Our study provides evidence for associations of later onset and steeper pubertal growth with greater maximally attained lung volumes by analysing longitudinal heights around the time of puberty using a validated approach for both males and females. We found that pubertal growth patterns associated with increased lung volumes were associated with reduced reporting of asthma-like symptoms in this population of young adults despite the absence of evidence of specific effects on airway obstruction. We have shown previously that low $FEV_1$ tracks through childhood and may be associated with COPD in adults (38, 39), but the long-term implications on adult lung disease of lung volume changes we observed during puberty without evidence of dysanaptic growth have yet to be fully determined.

Our findings, together with evidence of a secular trends towards earlier puberty (8), may have population-level consequences on lifetime lung function and respiratory symptoms and raise a public health implication for targeting modifiable childhood factors, such as obesity and overweight, that may contribute to pubertal growth patterns.

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## FIGURE LEGENDS

**Figure 1**. Flow chart of study subjects included in the analyses

**Figure 2**. Individual height growth curves for: (a) 4,772 males with 33,367 measurements; (c) 4,849 females with 33,783 measurements, from age 5 to 20 years. The mean curves, fitted by the SITAR models, of height growth (in solid black) and height velocity (in dashed blue) for: (b) males; (d) females are illustrated, with vertical lines (in dotted red) indicating mean pubertal age (13.5 and 11.7 years for males and females respectively). The right vertical axis in (b) and (d) represents the height velocity in (cm/year).

**Figure 3**. Adjusted differences (with 95% CI) in lung function measurements in adolescence (age 15 years) and early adulthood (age 24 years) associated with 1-year latter pubertal age.

Abbreviations: ml = millimetres; s = second; APV = pubertal age.

*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; birth weight; ever doctor-diagnosed asthma by age 14 years; exposure to smoke from birth to 8 years of age; smoking status.

**Figure 4**. Adjusted differences (with 95% CI) in lung function measurements in adolescence (age 15 years) and early adulthood (age 24 years) associated with 1-cm/year greater peak height velocity.

Abbreviations: ml = millimetres; s = second; PV = peak height velocity.
*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; birth weight; ever doctor-diagnosed asthma by age 14 years; exposure to smoke from birth to 8 years of age; smoking status.

## TABLES

Table 1. Characteristics of subjects by sex

| Characteristic | Male ($n_1 = 4,772$) | | Female ($n_2 = 4,849$) | | $P$‡ |
|---|---|---|---|---|---|
| | n | Percent or median (IQR) | n | Percent or median (IQR) | |
| **Potential confounders** | | | | | |
| Lower maternal education* | 2,553 | 59.5 | 2,567 | 59.8 | 0.778 |
| Having ≥1 sibling (parity) | 2,331 | 53.8 | 2,359 | 54.5 | 0.538 |
| Maternal history of asthma or allergy | 1,998 | 47.4 | 1,971 | 46.5 | 0.398 |
| Maternal smoking during pregnancy | 985 | 23.3 | 957 | 22.3 | 0.294 |
| Maternal anxiety during pregnancy† | 1,171 | 29.8 | 1,268 | 32.6 | 0.009 |
| Low birth weight (<2.5 kg) | 193 | 4.3 | 208 | 4.7 | 0.456 |
| Preterm delivery (<37 wk) | 267 | 5.9 | 213 | 4.7 | 0.010 |
| White ethnic group | 4,015 | 95.6 | 4,036 | 95.8 | 0.684 |
| Ever doctor-diagnosed asthma by age 14 y | 1,164 | 36.4 | 931 | 30.2 | $2\times10^{-7}$ |
| Day care attendance within first year | 272 | 6.7 | 253 | 6.3 | 0.438 |
| Exposure to smoke from birth to age 8 y | 2,452 | 64.7 | 2,505 | 66.7 | 0.063 |
| Smoking by 14 y | 454 | 18.6 | 966 | 31.0 | $2\times10^{-16}$ |
| Smoking by 23 y | 1,753 | 79.4 | 2,724 | 79.6 | 0.816 |
| **Control Variables** | | | | | |
| **Childhood spirometry:** | | | | | |
| FEV1 at age 8 y (L) | 3,325 | 1.73 (1.56 to 1.92) | 3,377 | 1.64 (1.49 to 1.80) | $2\times10^{-16}$ |
| FVC at age 8 y (L) | 3,325 | 1.98 (1.78 to 2.20) | 3,377 | 1.83 (1.65 to 2.03) | $2\times10^{-16}$ |
| $FEV_1$/FVC at age 8 y (%) | 3,325 | 88.0 (83.2 to 92.0) | 3,377 | 89.8 (85.8 to 93.4) | $2\times10^{-16}$ |
| $FEF_{25-75}$ at age 8 y (L/s) | 3,325 | 2.04 (1.67 to 2.39) | 3,377 | 2.07 (1.74 to 2.43) | 0.001 |
| **Variables at 15y:** | | | | | |
| Age (y) | 2,556 | 15.3 (15.3 to 15.5) | 2,856 | 15.4 (15.2 to 15.6) | $7\times10^{-4}$ |
| Height (m) | 2,535 | 1.75 (1.70 to 1.8) | 2,807 | 1.65 (1.61 to 1.70) | $2\times10^{-16}$ |
| **Variables at 24y:** | | | | | |
| Age (y) | 1,358 | 24.5 (24.0 to 25.1) | 2,169 | 24.4 (23.8 to 25.0) | 0.001 |
| Height (m) | 1,355 | 1.80 (1.75 to 1.84) | 2,151 | 1.66 (1.62 to 1.70) | $2\times10^{-16}$ |

*Abbreviations*: IQR = Interquartile range; kg = kilogram; wk = weeks; y = years; L = litre; s = second; m = metre.

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

†Anxious mothers were defined as being in the fourth quartile of the Crown-Crisp Experiential Index (40).

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

Table 2. Descriptive statistics of lung function outcomes in the study population and restricted to subjects with complete data on confounders and control variables by sex

| **Lung function outcomes** | **Median (IQR)** | | | |
|---|---|---|---|---|
| | **All subjects in study population** | | **Restricted to subjects with complete data on confounders* and control variables†** | |
| **Adolescence (age 15 y):** | **Males ($n_1 = 1{,}909$)** | **Females ($n_2 = 2{,}108$)** | **Males ($\acute{n}_1 = 1{,}177$)** | **Females ($\acute{n}_2 = 1{,}235$)** |
| $FEV_1$ (L) | 3.86 (3.32 to 4.37) | 3.10 (2.71 to 3.46) | 3.86 (3.32 to 4.36) | 3.09 (2.69 to 3.46) |
| FVC (L) | 4.23 (3.63 to 4.78) | 3.30 (2.88 to 3.69) | 4.20 (3.64 to 4.76) | 3.28 (2.90 to 3.68) |
| $FEV_1$/FVC (%) | 92.0 (87.2 to 96.7) | 94.4 (89.7 to 98.1) | 92.2 (87.5 to 96.8) | 94.2 (89.7 to 97.9) |
| $FEF_{25-75}$ (L/s) | 4.62 (3.85 to 5.45) | 4.04 (3.37 to 4.71) | 4.65 (3.88 to 5.46) | 3.99 (3.36 to 4.72) |
| **Early adulthood (age 24 y):** | **Males ($n_1 = 1{,}062$)** | **Females ($n_2 = 1{,}770$)** | **Males ($\acute{n}_1 = 567$)** | **Females ($\acute{n}_2 = 990$)** |
| $FEV_1$ (L) | 4.61 (4.19 to 5.04) | 3.36 (3.06 to 3.66) | 4.61 (4.17 to 5.04) | 3.37 (3.10 to 3.66) |
| FVC (L) | 5.50 (5.00 to 6.06) | 3.89 (3.53 to 4.24) | 5.49 (4.97 to 6.09) | 3.89 (3.55 to 4.25) |
| $FEV_1$/FVC (%) | 84.2 (80.3 to 87.7) | 86.9 (83.5 to 90.3) | 84.4 (80.6 to 87.9) | 86.7 (83.5 to 90.3) |
| $FEF_{25-75}$ (L/s) | 4.80 (4.04 to 5.55) | 3.82 (3.25 to 4.39) | 4.84 (4.06 to 5.59) | 3.84 (3.29 to 4.37) |

*Abbreviations*: IQR = Interquartile range; y = years; L = litre; s = second.

*Confounders: parity; maternal history of asthma or allergy; maternal smoking during pregnancy; birth weight; ever doctor-diagnosed asthma by age 14 years; exposure to smoke from birth to age of eight years; smoking status.

†Control variables: baseline lung function at eight years old; age and height at visit clinics in which outcomes, reported in the first column, were measured.

Table 3. Adjusted* associations of age at menarche and pubic hair development for females and males respectively with lung function measurements at 15 years and 24 years

| Lung function outcomes | Adolescence (age 15 y) | | | | Early adulthood (age 24 y) | | | |
|---|---|---|---|---|---|---|---|---|
| | Females (menarche†) ($n_1$ = 1,181) | | Males (pubic hair‡) ($n_1$ = 1,123) | | Females (menarche†) ($n_1$ = 943) | | Males (pubic hair‡) ($n_1$ = 529) | |
| | $\beta$ (95% CI) | $P$§ | $\beta$ (95% CI) | $P$§ | $\beta$ (95% CI) | $P$§ | $\beta$ (95% CI) | $P$§ |
| $FEV_1$ (ml) | -13 (-40 to 14) | 0.337 | -254 (-421 to -87) | 0.003 | 28 (7 to 48) | 0.009 | 227 (177 to 603) | $4\times10^{-4}$ |
| FVC (ml) | -8 (-35 to 19) | 0.558 | -335 (-516 to -154) | $3\times10^{-4}$ | 27 (2 to 52) | 0.036 | 283 (26 to 540) | 0.031 |
| $FEV_1$/FVC (%) | -0.1 (-0.4 to 0.3) | 0.606 | 0.4 (-1.3 to 2.1) | 0.620 | 0 (-0.3 to 0.3) | 0.827 | 2.4 (-0.1 to 4.8) | 0.055 |
| $FEF_{25-75}$ (ml/s) | -23 (-71 to 24) | 0.331 | -234 (-502 to 34) | 0.869 | 23 (-18 to 65) | 0.266 | 557(195 to 919) | 0.003 |

*Abbreviations*: $\beta$ = estimate of effect of 1-year increase in age at first menstrual bleeding for females or age at attainment of advanced pubic hair Tanner stage (>2) for males 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; birth weight; ever doctor-diagnosed asthma by age 14 years; exposure to smoke from birth to 8 years of age; smoking status.

†age at menarche: age at the first day of the first menstrual bleeding.

‡age at attainment of pubic hair Tanner stage > 2, estimated by parametric survival models (13) from interval-censored maternal and self-reported data collected annually on pubic hair Tanner staging.

§$P$-values from Wald test.

Table 4. Adjusted associations of pubertal age and magnitude of peak height velocity with risk of asthma symptoms and wheezing at ages 16 and 23 years by gender.

| **Pubertal height growth** | **Asthma symptoms** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Adolescence (age 16 y)** | | | | **Early adulthood (age 23 y)** | | | |
| | **Females ($n_1 = 1{,}703$)** | | **Males ($n_2 = 1{,}278$)** | | **Females ($n_1 = 1{,}758$)** | | **Males ($n_2 = 924$)** | |
| | **Adjusted OR (95% CI)*** | ***P*†** | **Adjusted OR (95% CI)*** | ***P*†** | **Adjusted OR (95% CI)*** | ***P*†** | **Adjusted OR (95% CI)*** | ***P*†** |
| Pubertal age (APV) | 0.72 (0.59 to 0.87) | $7\times10^{-4}$ | 0.85 (0.68 to 1.07) | 0.171 | 0.84 (0.67 to 1.07) | 0.156 | 0.85 (0.56 to 1.28) | 0.433 |
| Peak velocity (PV) | 0.79 (0.66 to 0.94) | 0.010 | 0.81 (0.66 to 0.98) | 0.033 | 0.77 (0.61 to 0.96) | 0.022 | 0.83 (0.59 to 1.17) | 0.277 |
| | **Wheezing** | | | | | | | |
| | **Adolescence (age 16 y)** | | | | **Early adulthood (age 23 y)** | | | |
| | **Females ($n_1 = 2{,}120$)** | | **Males ($n_2 = 1{,}564$)** | | **Females ($n_1 = 2{,}041$)** | | **Males ($n_2 = 1{,}128$)** | |
| | **Adjusted OR (95% CI)*** | ***P*†** | **Adjusted OR (95% CI)*** | ***P*†** | **Adjusted OR (95% CI)*** | ***P*†** | **Adjusted OR (95% CI)*** | ***P*†** |
| Pubertal age (APV) | 0.89 (0.75 to 1.05) | 0.152 | 0.97 (0.79 to 1.20) | 0.799 | 0.79 (0.66 to 0.94) | 0.009 | 0.88 (0.68 to 1.15) | 0.357 |
| Peak velocity (PV) | 0.88 (0.76 to 1.03) | 0.101 | 0.99 (0.82 to 1.18) | 0.892 | 0.78 (0.66 to 0.93) | 0.006 | 0.87 (0.69 to 1.10) | 0.247 |

*Abbreviations*: OR = odds ratio; CI = confidence interval; y = years.

*Adjusted for: parity; maternal history of asthma or allergy; maternal smoking during pregnancy; birth weight; exposure to smoke from birth to 8 years of age; smoking status.

†*P*-values from Wald test.

## FIGURES

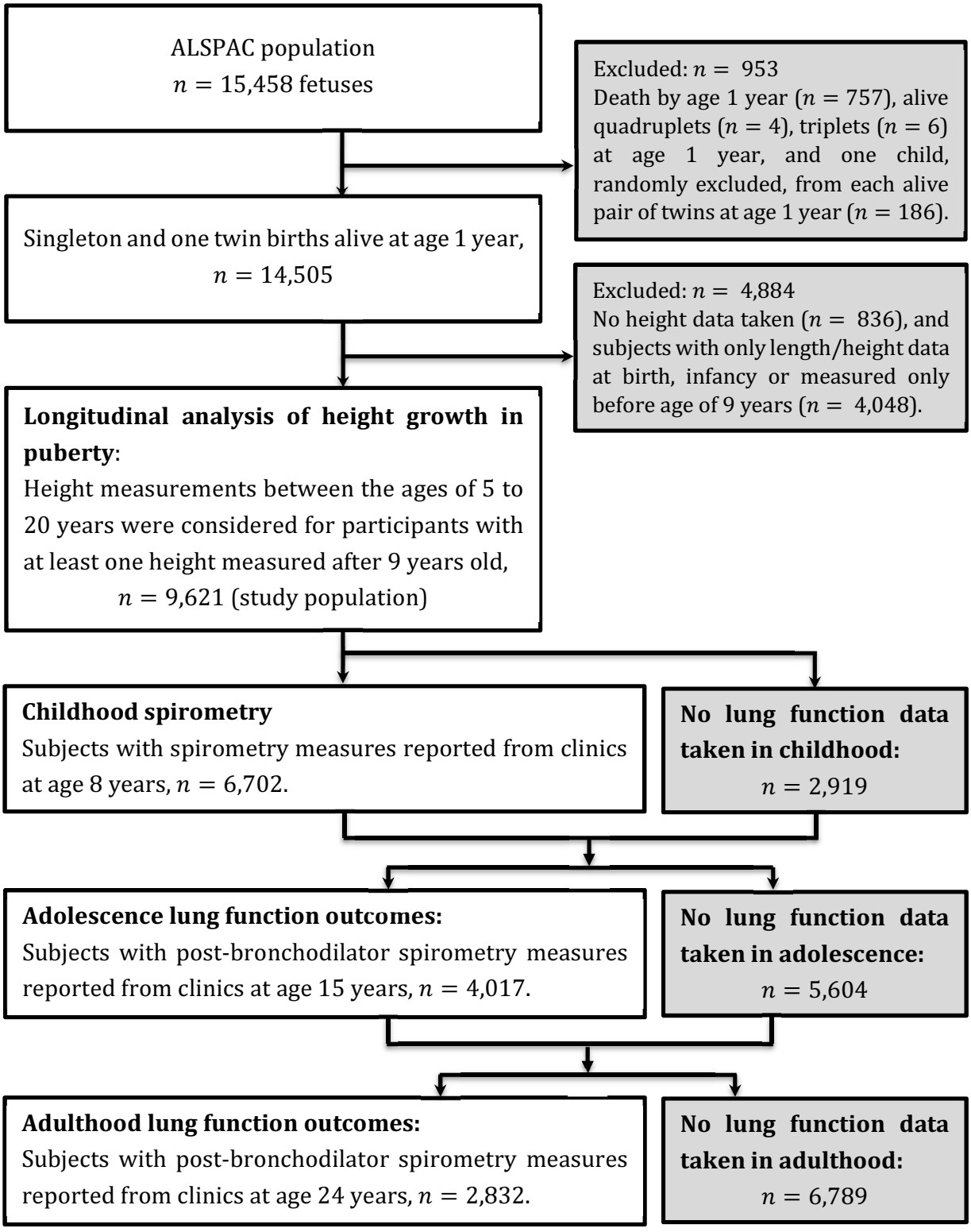
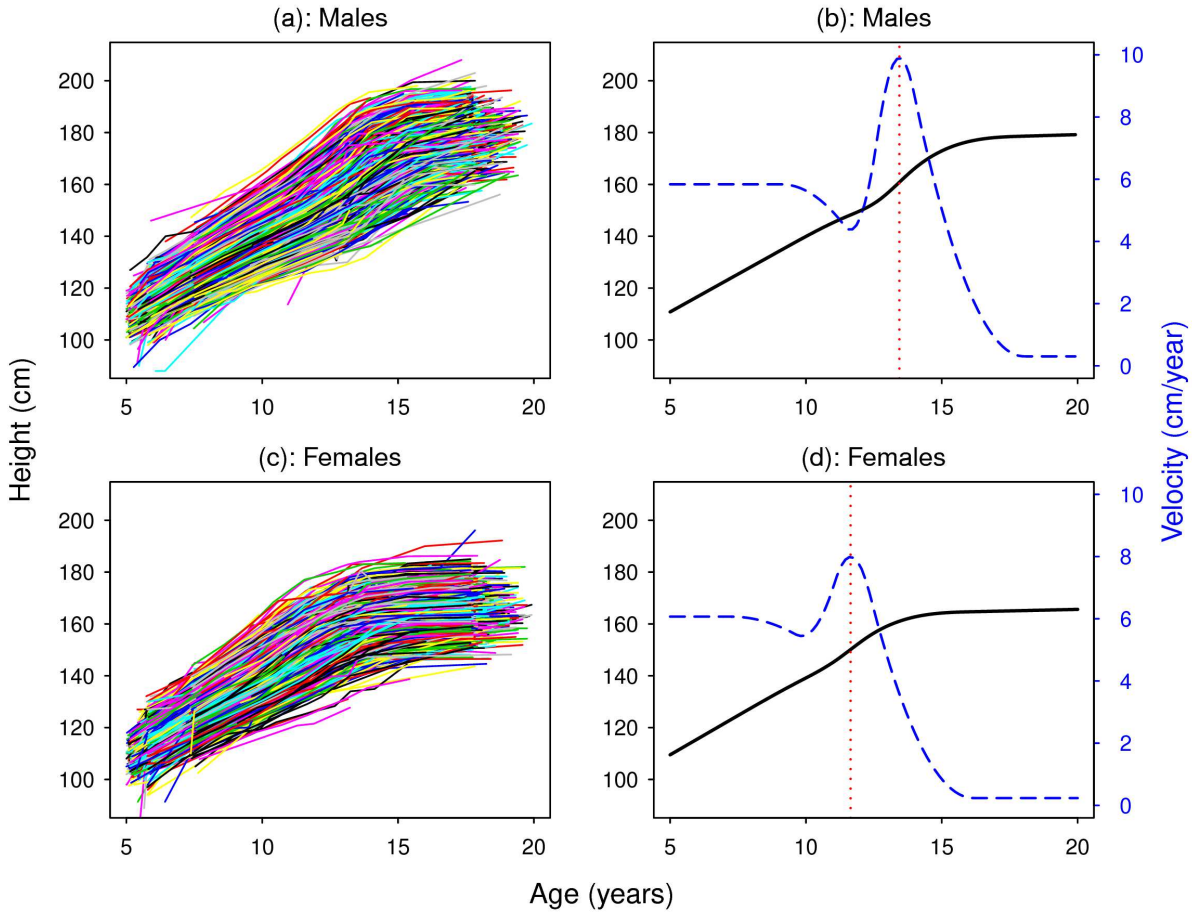



**Figure 1**. Flow chart of study subjects included in the analyses

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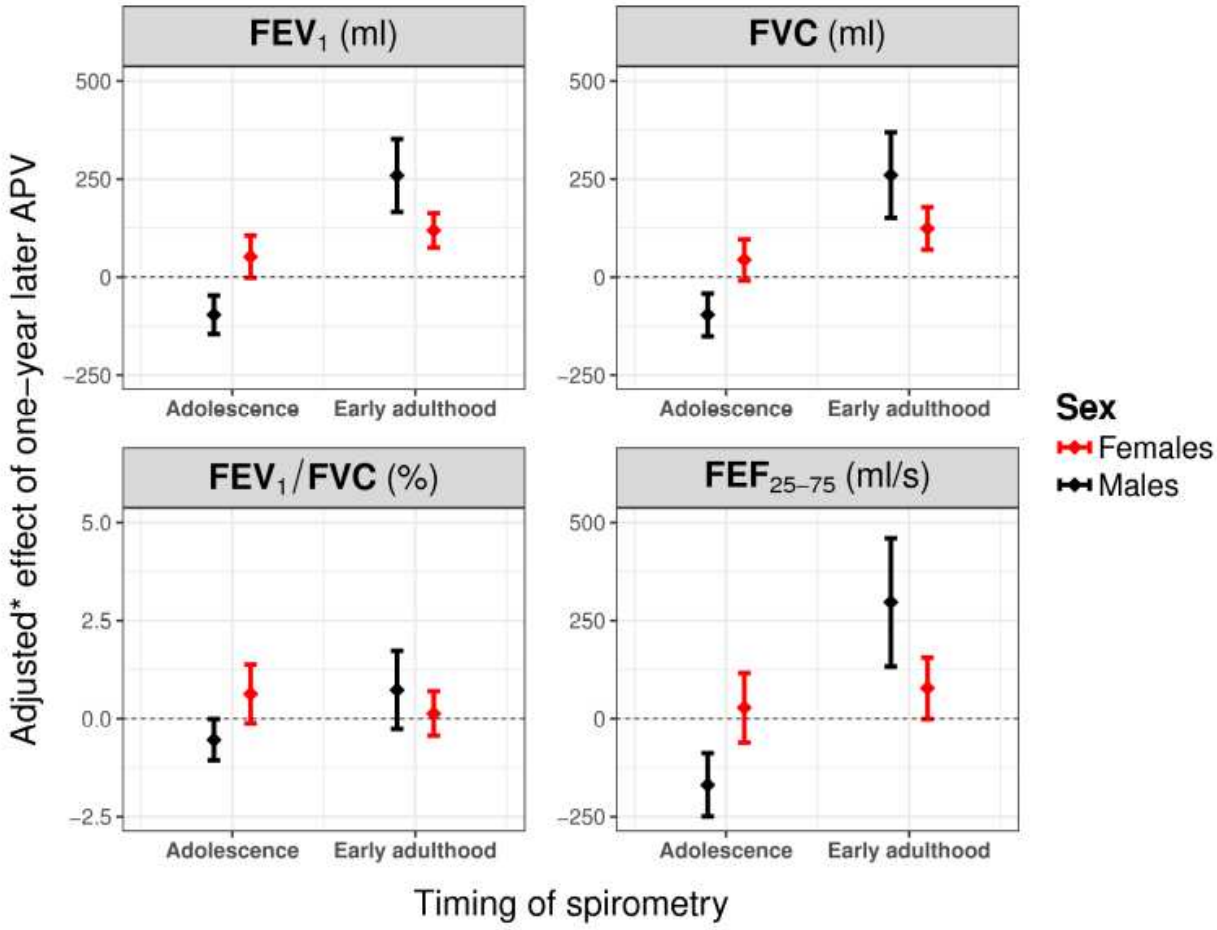


**Figure 3**. Adjusted differences (with 95% CI) in lung function measurements in adolescence (age 15 years) and early adulthood (age 24 years) associated with 1-year later pubertal age.

Abbreviations: ml = millilitres; s = second; APV = pubertal age.

*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; birth weight; ever doctor-diagnosed asthma by age 14 years; exposure to smoke from birth to 8 years of age; smoking status.

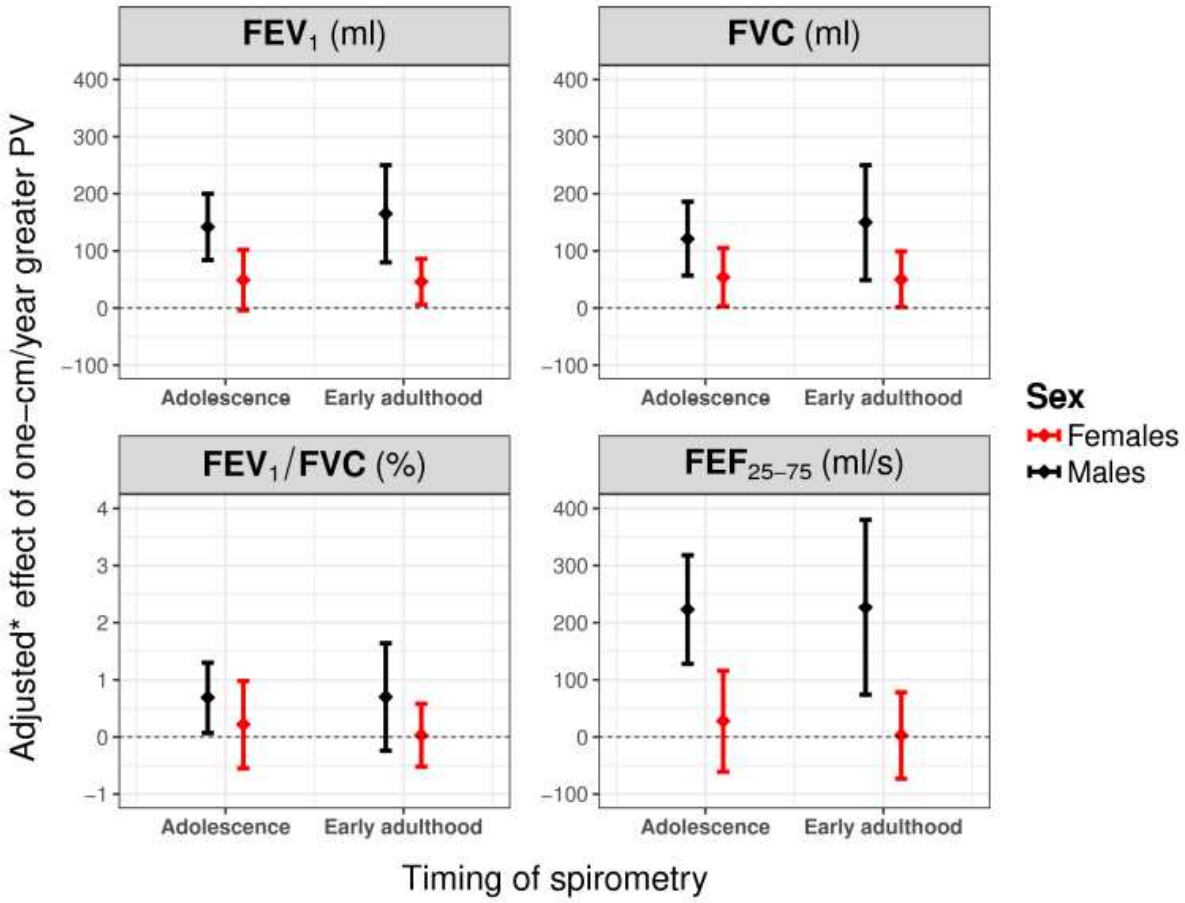


**Figure 4**. Adjusted differences (with 95% CI) in lung function measurements in adolescence (age 15 years) and early adulthood (age 24 years) associated with 1-cm/year greater peak height velocity.

Abbreviations: ml = millilitres; s = second; PV = peak velocity.

*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; birth weight; ever doctor-diagnosed asthma by age 14 years; exposure to smoke from birth to 8 years of age; smoking status.