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**Title: Association of asthma and smoking with lung function impairment in adolescence and early adulthood; the Isle of Wight Birth Cohort Study**

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**Abbreviations**

Chronic Obstructive Pulmonary Disease: COPD

Forced expiratory Volume in one second: FEV1

Forced Vital Capacity: FVC

Forced expiratory Volume in one second/Forced Vital Capacity: FEV1/FVC

Forced Expiratory Flow between 25-75: FEF25-75

Isle of Wight Birth Cohort: IOWBC

Post-bronchodilator (Post-BD)

Pre-bronchodilator (Pre-BD)

**Word Count:** 2826

**Take home:**

Asthma is associated with reduced lung function growth between 10-18 years while smoking is associated with decline between ages 18-26. Both may increase susceptibility to COPD, emphasising a potential benefit of early intervention to prevent lung damage.

**ABSTRACT**

We investigated associations of asthma and smoking with lung function and airway reversibility from childhood to early adulthood.

The population-based Isle of Wight Birth Cohort (n=1456) was assessed at birth, 1, 2, 4, 10, 18 and 26-years. Asthma was defined as physician diagnosis plus current wheeze and/or treatment. Spirometry was conducted at 10 (n=981), 18 (n=839) and 26 years (n=547). Individuals were subdivided into: non-smokers without asthma, non-smokers with asthma, smokers without asthma, and smokers with asthma, based on asthma and smoking status at age 26. Their lung function trajectories from 10 to 26 years were examined using longitudinal models.

Non-smokers with asthma had smaller FEV1, FEF25-75 and FEV1/FVC ratio compared to non-smokers without asthma at age 10 and 18, with differences reduced after bronchodilator (pre-bronchodilator FEV1 at 26-years: 3.75L versus 4.02L, P<0.001, post-bronchodilator 4.02L versus 4.16L, P= 0.08). This lung function deficit did not worsen after 18-years. Smokers without asthma had smaller FEF25-75 and FEV1/FVC ratio (but not FEV1) at 26-years compared to non-smokers without asthma with the deficit appearing after 18 years and persisting despite bronchodilator response (for FEV1/FVC ratio at 26-years: 0.80 versus 0.81, P=0.002; post-bronchodilator 0.83 versus 0.85, P=0.005). Smokers with asthma had worst lung function compared to other groups.

Lung function deficits associated with asthma and smoking occur early in life. They are not fully responsive to bronchodilator indicating a risk for long term lung health, which highlights the need to institute preventive measures in adolescence and early adult life before irreversible damage occurs.

**INTRODUCTION**

The normal trajectory of forced expiratory volume in one second (FEV1) shows age and height related growth during childhood and adolescence but age-related decline in adulthood (1). When exactly this decline starts might depend on factors such as sex, and on childhood conditions such as asthma (2, 3). A lower FEV1 strongly correlates with lifelong morbidity and higher mortality (4). Recent studies have also suggested that a low FEV1 (<80% predicted) in young adult life (<40 years of age) increases the risk of chronic obstructive pulmonary disease (COPD) several fold in later life, despite a normal age-related decline of lung function (5). Specifically, in smokers, FEV1 declines rapidly, resulting in irreversible airways obstruction (1, 6). However, there appears to be considerable variability in individual susceptibility to the deleterious effects of smoking on lung function (1). Identification of susceptible smokers early in the course of disease before irreversible damage occurs is vital for targeting preventive strategies like early smoking cessation which are known to slow age related decline in lung function (1).

Persistent childhood asthma is probably one of the major factors determining lower lung function and risk for fixed airflow obstruction in young adult life (7-9). Asthma may also increase susceptibility to deleterious effects of smoking (1). Those who smoke and/or have asthma in early adult life have increased risk of COPD, so it is important to investigate the relative contribution of these two exposures on the most sensitive lung function indices, and to establish when decline in lung function commences.

The Isle of Wight birth cohort (IOWBC) was examined at ages 10, 18 and 26-years for lung function and asthma, while information on environmental exposures, including active and passive smoking, were obtained since birth. In this study we determined the association of current asthma and smoking (assessed at age 26) with lung function from childhood to early adult life. We hypothesised that (i) lung function decline starts in childhood in those with asthma and by mid-twenties in those who smoke, and (ii) in smokers the resulting deficit has less bronchodilator reversibility compared to those with asthma.

**MATERIALS AND METHODS**

**Design and participants**

The Isle of Wight birth cohort is a prospective population-based cohort study investigating prevalence, natural history and risk and protective factors for the development of asthma, lung function and allergic diseases. All children (n=1536) born at St. Mary’s hospital on the Isle of Wight between 1st January 1989 and 28th February 1990 were enrolled with 1456 consenting for long term follow-up, which has so far been conducted at the ages of 1, 2, 4, 10, 18 and 26-years (10). The retention rate was >80% at all assessments up to 18 years and it was 71% at age 26. A wide range of phenotypic and environmental information has been collected using questionnaires and hospital medical records, study procedures such as skin prick test, spirometry, methacholine bronchial challenge and exhaled nitric oxide, and over 10,000 biological samples have been collected (Table S1). All participants provided informed consent and ethical approval was obtained from the local/national Research Ethics Committee at recruitment and at each assessment. At age 26, ethical approval was granted by National Research Ethics Committee, West Midlands (REC Reference: 15/WM/0071). The analysis and manuscript has followed the STROBE statement (11).

**Asthma and smoking assessment**

Validated questionnaires were completed at face to face interview or telephone/postal/web questionnaires. The majority of participants attending in person underwent spirometry at 10, 18, and 26-years and bronchodilator reversibility at 18 and 26-years. Details of questionnaires and other assessments have been reported previously (12, 13). Briefly, both study-specific and International Study of Asthma and Allergies in Childhood questionnaires were completed for detailed assessment of asthma symptoms and treatment. Current asthma was defined as physician diagnosis plus current wheeze and/or on treatment for wheeze/asthma. Information on environmental risk factors was collected from birth up to age 26-years including current and past cigarette smoking and asthma treatment use.

Four groups were defined and compared based on the presence of current asthma and/or current smoking at age 26-years. In this context, participants with a diagnosis of asthma at age 26, irrespective of previous status were regarded as having asthma. Similarly, those who were smoking at age 26, irrespective of previous smoking status were regarded as smoking. This gave 4 groups: (i) Non-smokers without asthma; (ii) Non-smokers with asthma; (iii) Smokers without asthma; and (iv) Smokers with asthma.

**Lung function assessment**

Pre-bronchodilator (pre-BD) spirometry was carried out at ages 10 (n=981), 18 (n=839) and 26-years (n=547) and post-bronchodilator (post-BD) spirometry at 18 (n=791) and 26-years (535), to allow assessment of changes in lung function over the rapid growth period of adolescence and to estimate early decline that might occur in high risk subpopulations due to underlying conditions, such as asthma or exposures, such as smoking. The subgroup with lung function data were not different in basic characteristics such as sex, smoking and allergic history to all the cohort members who participated at 26-year assessment (Table S2). For spirometry, American Thoracic Society (ATS) guidelines were followed to ensure validity and reproducibility (14). Koko Spirometers (Longmont, CO, USA; <http://www.nspirehealth.com/products/koko-testing-devices/koko-sx-1000-spirometer/>) with calibration performed at least once daily were used. To perform spirometry, participants had to be free from respiratory infection for 14 days, not taking oral steroids, not taken beta2 agonist for 6 hours and abstained from caffeine intake for at least 4 hours. Spirometry was performed with participants standing without nose-clip. The acceptability criteria for each effort included a satisfactory start and end of test as well as a plateau in the volume–time curve (14). FEV1, forced vital capacity (FVC), FEV1/FVC ratio, forced expiratory volume between 25 and 75 percent flow (FEF25-75) were recorded. As recommended, the highest of three FEV1 measurements within 5% of each other was used. Changes in FEV1, FEV1/FVC ratio, and FEF25-75 between assessments were calculated as the difference between values at 10 and 18 and then 18 and 26 years. Percent predicted for age, height, sex and ethnic origin was calculated for the FEV1, FVC, FEV1/FVC, and FEF25-75 based on Global Lung Initiative (GLI) reference equations (15). Bronchodilator reversibility was performed at 18 and 26 years. Post-BD values were obtained 20 minutes after inhalation of 600mcg salbutamol using a metered dose inhaler via a large volume spacer. Significant reversibility was defined as ≥12% increase in FEV1.

**Statistical analysis**

To examine associations between these four groups, longitudinal models were utilised. These longitudinal models were applied and inferred using generalised estimating equations (GEE) to give population averaged estimates. Models included sex, time and asthma/smoking group plus their interaction terms as adjusting factors. The dependent, lung function parameters, were estimated for 10 to 18 and 18 to 26-year timeframes adjusted to sex to maximise the number of participants included. As sensitivity analyses, we firstly repeated the analysis with the 10, 18 and 26 year time points in one model and secondly controlled for height at assessment by using percentage predicted lung function parameters (see online supplement). To examine the change in lung function parameters in individual participants, a regression model was used controlling for sex. STATA v14 (StataCorp, College Station, USA) was used for these data analyses. A p-value <0.05 was taken to indicate statistical significance.

**RESULTS**

Based on their asthma and smoking status at 26-years, there were 600 (58.3%) non-smokers without asthma, 108 (10.5%) non-smokers with asthma, 270 (26.2%) smokers without asthma, and 52 (5.0%) smokers with asthma. Characteristics of non-smokers with asthma, smokers without asthma and smokers with asthma at age 26-years are provided in Table S1. Mean age for smoking initiation was 16-years and thus most smokers had approximately 10-years of personal smoking duration. Table S3 provides lung function data at 10, 18 and 26 stratified by sex.

**Differences in lung function between groups at each assessment (10, 18 and 26-years)**

Looking at the longitudinal model, non-smokers with asthma compared to non-smokers without asthma at 26-years had a smaller pre-BD FEV1 and FEF25-75 at 18 and 26-years (around 9%) and FEV1/FVC ratio at all assessments (Table 1a and Figure 1). With narrowing of the difference following bronchodilator, the statistical significance of the difference was lost at 26 for Post-BD FEV1 and FEV1/FVC ratio. FEV1/FVC and FEF25-75 were lower in smokers without asthma (3.76 vs 4.05L, p<0.001 and 0.80 vs 0.81, p=0.002 respectively), compared to control, with the difference persisting after bronchodilation (Table 1b). Apart from FVC, all lung function parameters in smokers with asthma at 26-years were much lower than for non-smokers without asthma, even after bronchodilator (Table 1c).

Smokers with asthma show proportionately less bronchodilator reversibility for FEV1/FVC and for FEF25-75 than non-smokers with asthma (Table 1d). In contrast, both pre- and post-BD FEV1, FEV1/FVC and FEF25-75 were smaller at the 26-year assessment in smokers with asthma compared to smokers without asthma (Table 1e). The pattern of lung function remain the same in the four groups in the subset which included participants with lung function data at all three time points (Figure S1). A sensitivity analysis on these participants using percent predicted values revealed no important changes in lung function trajectories (Figure S2).

**Changes in lung function across adolescence and early adulthood**

Non-smokers with asthma had a smaller increase in FEV1 (10 to 18 years change; 1.84 vs 2.06L, p<0.001, and FEF25-75 (10 to 18 change; 1.82 vs 2.13L, P<0.01), when compared to non-smokers without asthma, over adolescence but not between 18 and 26 in the longitudinal model (Figure 2). Smokers without asthma hada larger drop in FEF25-75 (-0.73 vs -0.50L, p<0.05) only between 18 and 26 years. FEV1 and FEF25-75 increased less over adolescence in smokers with asthma compared to non-smokers without asthma (1.77 vs 2.06L, p<0.01 and 1.48 vs 2.13L, p<0.001 respectively). Comparing further between groups, non-smokers with asthma had a smaller increase in FEV1 and FEF25-75 over adolescence than smokers without asthma (1.75 vs 1.95L, p<0.01 and 1.71 vs 1.98, p<0.05 respectively).

**DISCUSSION**

We examined longitudinal trajectories of lung function from age 10 to 26 in participants who were smoking and/or had asthma at age 26. Non-smokers with asthma at 26-years had a smaller FEV1, FEF25-75 and FEV1/FVC ratio in young adulthood with differences reduced after bronchodilator. This deficit in lung function appeared during childhood and over adolescence but did not get worse after 18-years. In smokers without asthma, there was no difference in FEV1, although FEF25-75 and FEV1/FVC ratio were lower at 26-years with the differences appearing after 18-years and showing less bronchodilator reversibility than that seen in asthma. Smokers with asthma tended to have the worst lung function.

Our study confirms that the decline in indices of lung function reflecting airway diameter (FEV1/FVC and FEF25-75) occurs early in adult life. While some of the apparent deficit in lung function observed in those with asthma at 26 is reversible, there remains a degree of reduced lung function following bronchodilator suggesting that asthma is associated with suboptimal lung growth during adolescence, the lack of complete reversibility to bronchodilator or both. Smoking young adults show a decline in lung function developing in the early twenties, which improves with bronchodilator but remains lower than non-smokers, indicating future potential risk of COPD. This indicates that adolescence and early adult life is a crucial period where intervention such as improved asthma treatment and smoking cessation might interrupt a downward trajectory, which otherwise could lead to fixed airflow limitation.

Asthma increases the risk of COPD later in life (16). We and others have shown that long term trajectories of FEV1 include the level of maximum lung function achieved and the onset and rate of subsequent decline (17, 18). However, the study of Bui et al (17) was only recruited at 7 years of age limiting the quality of the early life data. The age of onset of FEV1 decline is reported variably between 20 and 30-years while the decline in FEV1/FVC starts in childhood even in those without asthma or smoking exposure (3, 19). Therefore, COPD could result from lack of attaining optimal lung function in early adulthood as suggested by Lange et al (5). We also showed that young adults with asthma do not achieve optimal lung function by 18-years of age, which might put them at higher risk of future COPD. However, the subsequent rate of decline between 18 and 26 was similar to those who did not have asthma at 26 and reversibility to bronchodilator was present. McGeachie et al showed that subgroups within those with asthma behave differently and some are more likely to have lower lung function as they go into adult life than others (9). Grol et al examined factors determining FEV1 decline among those with asthma (20). However, neither of these studies had a control group of no asthma for comparison and they did not look specifically for the effect of smoking.

James et al. studied the association of both asthma and smoking on lung function (21). FEV1 was lower at age 19 with asthma but not in smokers; however, those with asthma and smoking had the worst outcome with later follow-up confirming their more rapid decline in FEV1. This is consistent with our study where smoking participants with asthma have worst lung function and are less response to bronchodilator. Aanerud et al found a 20 fold increase in the risk of adult airway obstruction in early-onset asthma (22). This is supported by our observation of lower lung function at age 10 years in those with asthma at age 26 years, highlighting the importance of asthma as a major determinant of lower lung function trajectory during adolescence and adult life.

We analysed FEF25-75 as an indicator of small airway disease which is affected early in smoking related lung disease (23). The FEF25-75 paralleled changes in FEV1/FVC ratio and was highly sensitive to changes occurring with age and with smoking and asthma. Previous studies showed a decline in FEV1 in smokers starting in their mid-twenties or later (1, 24, 25). Using FEF25-75 we have shown that the decline starts earlier than previously thought with impairment by the mid-twenties despite preserved bronchodilator reversibility.

Belgrave et al. examined childhood trajectories of FEV1, and showed that the persistently low FEV1 trajectory is associated with severe wheezing exacerbations, early allergic sensitisation and tobacco smoke exposure in early life (26). Results from the Tucson birth cohort also identified a low lung function trajectory in early adult life, predisposed by maternal asthma, early life lower respiratory illness and current asthma (27). In contrast, we have focussed on adolescent and early adult life factors of asthma and smoking exposure.

The strengths of our study include prospective follow-up from birth, homogenous population, extensive characterisation including standardized questionnaires and high retention, thus avoiding misclassification. We defined our asthma and smoking groups based on participants’ status at 26-years. Asthma is a dynamic condition where some people improve while others develop asthma at various ages. Similarly, smoking status can change over time. Thus, not all those defined as having asthma and smokers in this study, had asthma or were smoking between 10 and 26-years. Sample size constraints did not allow further subgroups based on duration of asthma or smoking. However, the purpose of this analysis was to focus on those who were smoking or had asthma or both in their young adult life, and retrospectively look at their lung function pattern in order to assess their risk of future respiratory health, particularly potential risk of COPD. Another potential limitation is of recall bias as smokers with asthma were assessed using questionnaires. However, as we defined asthma and smoking status at age 26, recall bias is less likely.

In our cohort, the decline in FEV1/FVC occurred in all groups but it was most prominent between 18 and 26 years and worst in smokers with asthma at 26 (Figures 1, 2). Given that the normal range of this ratio changes with age (15, 28), an FEV1/FVC of 0.75 would be considered abnormal at 30 years of age. It is therefore concerning to note that 39 (7.3%) participants in our cohort had a post-bronchodilator FEV1/FVC of <0.75 at age 26-years. Further assessment of this cohort should focus on this group to get a more detailed assessment of their respiratory health, with full lung function tests and imaging to assess signs of structural damage.

In summary, (i) presence of asthma at the age of 26 years in non-smokers and smokers is associated with a lower lung function, which can be tracked back to the ages of 10 and 18 years, (ii) presence of smoking at the age of 26 years in non-asthmatics and asthmatics is associated with a lower lung function, which can be tracked back to the age of 18 years, and (iii) individuals with a combination of asthma and smoking at the age of 26 years had worst lung function. There was less bronchodilator reversibility in smokers than those with asthma. Early identification of those who are at high risk of COPD, due to asthma, smoking or both, should provide a focus for strategies aimed at preventing long term lung damage and future morbidity.

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**Figure Legends**

**Figure 1**

Figures describe the mean value of each lung function parameter at 10, 18 and 26 years of age in smokers with asthma (open triangle), non-smokers with asthma (open circles), smokers without asthma (closed triangle) and non-smokers without asthma (closed circles). Data generated from a GEE longitudinal modelling with parameters adjusted for sex. Points represent means with 95% confidence intervals. Post-bronchodilator parameters only available at 18 and 26 years. Data from 10 to 18 years represents results available for 699 participants with data at each point; for the 18 to 26 years analysis, results available for 454 participants; post-bronchodilator results available for 428 participants.

**Figure 2**

Figures describe the change in each lung function parameter from 10 to 18 and from 18 to 26 years of age in smokers with asthma (open triangle), non-smokers with asthma (open circles), smokers without asthma (closed triangle) and non-smokers without asthma (closed circles).Figures generated from a regression model with parameters adjusted for sex. Points represent means change in lung function with 95% confidence intervals. Dashed line indicated zero change. P-values for comparisons between groups \*: p<0.05, \*\*: p<0.01, \*\*\*: p<0.001. Post-bronchodilator parameters only available at 18 and 26 years. Data from 10 to 18 years represents results from 699 participants with data at each point; for the 18 to 26 years analysis, results are from 454 participants; post-bronchodilator results available for 428 participants.

**Table 1: Association of asthma and smoking status on pre- and post-bronchodilator spirometry at 10, 18 and 26 years of age**

**(a) Non-smokers with asthma versus non-smokers without asthma participants**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **10 years** |  | **18 years** |  | **26 years** |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Non-smokers without asthma****N=422**  | **Non-smokers with asthma** **N=80** | **Difference** | **P value** |  | **Non-smokers without asthma****N=417**  | **Non-smokers with asthma****N=74**  | **Difference** | **P value** |  | **Non-smokers without asthma****N=313**  | **Non-smokers with asthma****N=62**  | **Difference** | **P value** |
| **FEV1 (L)** | 2.04 | 2.00 | -0.05(-0.16, 0.04) | 0.273 |  | 4.05 | 3.77 | -0.27(-0.37, -0.17) | <0.001 |  | 4.02 | 3.75 | -0.28(-0.41, -0.14) | <0.001 |
| **Post-FEV1 (L)** |  |  |  |  |  | 4.18 | 4.02 | -0.16(-0.30, -0.02) | 0.023 |  | 4.16 | 4.02 | -0.13(-0.28, 0.02) | 0.078 |
| **FVC (L)** | 2.30 | 2.31 | 0.00(-0.12, 0.12) | 0.984 |  | 4.60 | 4.46 | -0.14 (-0.26, 0.02) | 0.024 |  | 4.96 | 4.90 | -0.06(-0.22, 0.11) | 0.497 |
| **Post-FVC (L)** |  |  |  |  |  | 4.63 | 4.56 | -0.08(-0.24, 0.08) | 0.322 |  | 4.92 | 4.87 | -0.06 (-0.22, 0.11) | 0.510 |
| **FEV1/FVC** | 0.89 | 0.87 | -0.03(-0.04, -0.01) | <0.001 |  | 0.88 | 0.85 | -0.03(-0.05, -0.02) | <0.001 |  | 0.81 | 0.77 | -0.04(-0.06, -0.03) | <0.001 |
| **Post- FEV1/FVC** |  |  |  |  |  | 0.91 | 0.89 | -.02(-0.03, -0.01) | 0.021 |  | 0.85 | 0.83 | -0.02(-0.03, 0.00) | 0.052 |
| **FEF25-75 (L)** | 2.49 | 2.25 | -0.25(-0.440, -0.059) | 0.010 |  | 4.56 | 4.00 | -0.56(-0.75, -0.36) | <0.001 |  | 4.05 | 3.31 | -0.75(-1.01, -0.49) | <0.001 |
| **Post FEF25-75 (L)** |  |  |  |  |  | 4.98 | 4.56 | -0.42(-0.67, -0.17) | 0.001 |  | 4.64 | 4.24 | -0.40(-0.67, -0.13) | 0.004 |

**(b) Smokers without asthma versus non-smokers without asthma participants**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **10 years** |  | **18 years** |  | **26 years** |
|  | **Non-smokers without asthma****N=422**  | **Smokers without asthma****N=203** | **Difference** | **P value** |  | **Non-smokers without asthma N=417** | **Smokers without asthma****N=176** | **Difference** | **P value** |  | **Non-smokers without asthma****N=313**  | **Smokers without asthma****N=142** | **Difference** | **P value** |
| **FEV1 (L)** | 2.04 | 2.03 | -0.02(-0.09, 0.05) | 0.526 |  | 4.05 | 4.00 | -0.05(-0.12, 0.02) | 0.149 |  | 4.02 | 3.93 | -0.10(-0.19, 0.00) | 0.052 |
| **Post-FEV1 (L)** |  |  |  |  |  | 4.18 | 4.18 | 0.00(-0.10, 0.10) | 0.975 |  | 4.16 | 4.08 | -0.08(-0.18, 0.02) | 0.131 |
| **FVC (L)** | 2.30 | 2.28 | -0.03(-0.11, 0.05) | 0.506 |  | 4.60 | 4.59 | -0.02 (-0.10, 0.06) | 0.617 |  | 4.96 | 4.97 | 0.01(-0.10, 0.12) | 0.863 |
| **Post-FVC (L)** |  |  |  |  |  | 4.63 | 4.66 | 0.03(-0.09, 0.14) | 0.643 |  | 4.92 | 4.93 | 0.00(-0.11, 0.12) | 0.970 |
| **FEV1/FVC** | 0.89 | 0.89 | 0.00(-0.01, 0.01) | 0.645 |  | 0.88 | 0.87 | -0.01(-0.02, 0.00) | 0.075 |  | 0.81 | 0.80 | -0.02(-0.03, -0.01) | 0.002 |
| **Post- FEV1/FVC** |  |  |  |  |  | 0.91 | 0.90 | -0.01(-0.02, 0.01) | 0.359 |  | 0.85 | 0.83 | -0.02(-0.03, -0.01) | 0.005 |
| **FEF25-75 (L)** | 2.49 | 2.44 | -0.05(-0.18, 0.08) | 0.465 |  | 4.56 | 4.47 | -0.10(-0.23, 0.04) | 0.157 |  | 4.05 | 3.76 | -0.31(-0.49, -0.13) | 0.001 |
| **Post FEF25-75 (L)** |  |  |  |  |  | 4.98 | 4.90 | -0.09(-0.27, 0.08) | 0.299 |  | 4.64 | 4.38 | -0.27(-0.46, -0.09) | 0.004 |

**(c) Smokers with asthma versus non-smokers without asthma participants**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **10 years** |  | **18 years** |  | **26 years** |
|  | **Non-smokers without asthma****N= 422** | **Smokers with asthma****N=40**  | **Difference** | **P value** |  | **Non-smokers without asthma****N=417**  | **Smokers with asthma****N=32** | **Difference** | **P value** |  | **Non-smokers without asthma****N=313**  | **Smokers with asthma****N=30** | **Difference** | **P value** |
| **FEV1 (L)** | 2.04 | 2.01 | -0.04(-0.18, 0.08) | 0.469 |  | 4.05 | 3.73 | -0.33(-0.48, -0.19) | <0.001 |  | 4.02 | 3.74 | -0.30(-0.49, -0.12) | 0.001 |
| **Post-FEV1 (L)** |  |  |  |  |  | 4.18 | 4.03 | -0.17(-0.36, 0.02) | 0.080 |  | 4.16 | 3.95 | -0.23(-0.42, -0.03) | 0.021 |
| **FVC (L)** | 2.30 | 2,32 | 0.01 (-0.14, 0.17) | 0.858 |  | 4.60 | 4.60 | -0.01(-0.18, 0.16) | 0.894 |  | 4.96 | 4.96 | 0.00(-0.22, 0.22) | 0.99 |
| **Post-FVC (L)** |  |  |  |  |  | 4.63 | 4.72 | 0.08(-0.14, 0.30) | 0.483 |  | 4.92 | 5.03 | 0.11(-0.12, 0.33) | 0.351 |
| **FEV1/FVC** | 0.89 | 0.86 | -0.03(-0.05, -0.01) | 0.002 |  | 0.88 | 0.82 | -0.06(-0.09, -0.04) | <0.001 |  | 0.81 | 0.76 | -0.06(-0.08, -0.04) | <0.001 |
| **Post- FEV1/FVC** |  |  |  |  |  | 0.91 | 0.86 | -0.05(-0.07, -0.03) | <0.001 |  | 0.85 | 0.79 | -0.06(-0.08, -0.04) | <0.001 |
| **FEF25-75 (L)** | 2.49 | 2.22 | -0.28(-0.54, -0.03) | 0.027 |  | 4.56 | 3.66 | -0.93(-1.21, -0.65) | <0.001 |  | 4.05 | 3.15 | -0.93(-1.28, -0.59) | <0.001 |
| **FEF25-75 Post (L)** |  |  |  |  |  | 4.98 | 4.30 | -0.74(-1.09, -0.38) | <0.001 |  | 4.64 | 3.67 | -1.00(-1.36, -0.65) | <0.001 |

**(d) Smokers with asthma versus non-smokers with asthma participants**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **10 years** |  | **18 years** |  | **26 years** |
|  | **Non-smokers with asthma****N=80** | **Smokers with asthma****N=40** | **Difference** | **P value** |  | **Non-smokers with asthma****N=74** | **Smokers with asthma****N=32** | **Difference** | **P value** |  | **Non-smokers with asthma****N=62** | **Smokers with asthma** **N=30** | **Difference** | **P value** |
| **FEV1 (L)** | 2.00 | 2.01 | 0.01(-0.15, 0.17) | 0.930 |  | 3.77 | 3.73 | -0.06(-0.23, 0.11) | 0.483 |  | 3.75 | 3.74 | -0.03(-0.24, 0.19) | 0.813 |
| **Post-FEV1 (L)** |  |  |  |  |  | 4.02 | 4.03 | -0.01(-0.23, 0.21) | 0.925 |  | 4.02 | 3.95 | (-0.09(-0.32, 0.13) | 0.414 |
| **FVC (L)** | 2.31 | 2.32 | 0.02(-0.17, 0.20) | 0.869 |  | 4.46 | 4.60 | 0.13 (-0.07, 0.32) | 0.215 |  | 4.90 | 4.96 | 0.06(-0.20, 0.31) | 0.676 |
| **Post-FVC (L)** |  |  |  |  |  | 4.56 | 4.72 | 0.16(-0.10, 0.42) | 0.225 |  | 4.87 | 5.03 | 0.16 (-0.10, 0.43) | 0.227 |
| **FEV1/FVC** | 0.87 | 0.86 | -0.01(-0.03, 0.02) | 0.690 |  | 0.85 | 0.82 | -0.03(-0.06, 0.00) | 0.022 |  | 0.77 | 0.76 | -0.02(-0.04, 0.01) | 0.312 |
| **Post- FEV1/FVC** |  |  |  |  |  | 0.89 | 0.86 | -0.03(-0.06, -0.01) | 0.013 |  | 0.83 | 0.79 | -0.04(-0.07, -0.02) | 0.001 |
| **FEF25-75 (L)** | 2.25 | 2.22 | -0.04(-0.33, 0.26) | 0.817 |  | 4.00 | 3.66 | -0.36(-0.70, -0.05) | 0.022 |  | 3.31 | 3.15 | -0.17(-0.590, 0.225) | 0.379 |
| **FEF25-75 Post (L)** |  |  |  |  |  | 4.56 | 4.30 | -0.30(-0.73, 0.09) | 0.130 |  | 4.24 | 3.67 | -0.59(-1.03, -0.19) | 0.005 |

**(e) Smokers with asthma versus smokers without asthma participants**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **10 years** |  | **18 years** |  | **26 years** |
|  | **Smokers without asthma N=203** | **Smokers with asthma N=40** | **Difference** | **P value** |  | **Smokers without asthma N=176**  | **Smokers with asthma N=32**  | **Difference** | **P value** |  | **Smokers without asthma N=142**  | **Smokers with asthma N=30**  | **Difference** | **P value** |
| **FEV1 (L)** | 2.03 | 2.01 | -0.03(-0.17, 0.11) | 0.704 |  | 4.00 | 3.73 | -0.28(-0.43, -0.13) | <0.001 |  | 3.93 | 3.74 | -0.21(-0.40, -0.01) | 0.036 |
| **Post-FEV1 (L)** |  |  |  |  |  | 4.18 | 4.03 | -0.17(-0.37, 0.03) | 0.098 |  | 4.08 | 3.95 | -0.15(-0.35, 0.06) | 0.153 |
| **FVC (L)** | 2.28 | 2,32 | 0.04 (-0.12, 0.20) | 0.618 |  | 4,59 | 4,60 | 0.01 (-0.17, 0.19) | 0.916 |  | 4.97 | 4.96 | -0.01(-0.24, 0.22) | 0.922 |
| **Post-FVC (L)** |  |  |  |  |  | 4.66 | 4.71 | 0.05(-0.18, 0.29) | 0.658 |  | 4.93 | 5.03 | 0.10 (-0.13, 0.34) | 0.386 |
| **FEV1/FVC** | 0.89 | 0.86 | -0.03(-0.05, -.009) | 0.006 |  | 0.87 | 0.82 | -0.05(-0.08, -0.03) | <0.001 |  | 0.80 | 0.76 | -0.04(-0.064, -0.013) | 0.003 |
| **Post- FEV1/FVC** |  |  |  |  |  | 0.90 | 0.86 | -0.05(-0.07, -0.02) | <0.001 |  | 0.83 | 0.79 | -0.04(-0.07, -0.02) | <0.001 |
| **FEF25-75 (L)** | 2.44 | 2.22 | -0.24-0.50, 0.03) | 0.081 |  | 4.47 | 3.66 | -0.84(-1.13, -0.54) | <0.001 |  | 3.76 | 3.15 | -0.62(-0.99, -0.26) | 0.001 |
| **FEF25-75 Post (L)** |  |  |  |  |  | 4.90 | 4.30 | -0.64(-1.01, -0.27) | 0.001 |  | 4.38 | 3.67 | -0.73(-1.10, -0.36) | <0.001 |

Figures represent mean spirometry parameters pre- and post-salbutamol with mean difference (95% confidence interval) and associated p-value from longitudinal modelling. Results divided according to asthma and smoking status at 26 years; (i) Non-smokers without asthma, (ii) Non-smokers with asthma, (iii) Smokers without asthma, (iv) Smokers with asthma. Results for 10 and 18 years from GEE longitudinal model for 10 to 18 years adjusted for sex; results for 26 years from a similar model for 18 to 26 year data. Differences may not add up due to rounding. Post-bronchodilator parameters only available at 18 and 26 years. Data from 10 to 18 years represents results available for 699 participants with data at each point; for the 18 to 26 years analysis, results available for 454 participants; post-bronchodilator results available for 428 participants.

**References**

1. Kohansal R, Martinez-Camblor P, Agusti A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. American journal of respiratory and critical care medicine. 2009;180(1):3-10.

2. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. The American review of respiratory disease. 1983;127(6):725-34.

3. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A Longitudinal, Population-Based, Cohort Study of Childhood Asthma Followed to Adulthood. New England Journal of Medicine. 2003;349(15):1414-22.

4. Young RP, Hopkins R, Eaton TE. Forced expiratory volume in one second: not just a lung function test but a marker of premature death from all causes. The European respiratory journal. 2007;30(4):616-22.

5. Lange P, Celli B, Agusti A, Boje Jensen G, Divo M, Faner R, et al. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. The New England journal of medicine. 2015;373(2):111-22.

6. Fletcher C, Peto R. The natural history of chronic airflow obstruction. British medical journal. 1977;1(6077):1645-8.

7. Duijts L, Reiss IK, Brusselle G, de Jongste JC. Early origins of chronic obstructive lung diseases across the life course. European journal of epidemiology. 2014;29(12):871-85.

8. Guerra S, Stern DA, Zhou M, Sherrill DL, Wright AL, Morgan WJ, et al. Combined effects of parental and active smoking on early lung function deficits: a prospective study from birth to age 26 years. Thorax. 2013;68(11):1021-8.

9. McGeachie MJ, Yates KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, et al. Patterns of Growth and Decline in Lung Function in Persistent Childhood Asthma. The New England journal of medicine. 2016;374(19):1842-52.

10. Arshad SH, Holloway JW, Karmaus W, Zhang H, Ewart S, Mansfield L, et al. Cohort Profile: The Isle Of Wight Whole Population Birth Cohort (IOWBC). Int J Epidemiol. 2018;47(4):1043-4i.

11. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Journal of clinical epidemiology. 2008;61(4):344-9.

12. Balte P, Karmaus W, Roberts G, Kurukulaaratchy R, Mitchell F, Arshad H. Relationship between birth weight, maternal smoking during pregnancy and childhood and adolescent lung function: A path analysis. Respiratory medicine. 2016;121:13-20.

13. Scott M, Raza A, Karmaus W, Mitchell F, Grundy J, Kurukulaaratchy RJ, et al. Influence of atopy and asthma on exhaled nitric oxide in an unselected birth cohort study. Thorax. 2010;65(3):258-62.

14. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. The European respiratory journal. 2005;26(2):319-38.

15. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. The European respiratory journal. 2012;40(6):1324-43.

16. Postma DS, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. Lancet (London, England). 2015;385(9971):899-909.

17. Bui DS, Lodge CJ, Burgess JA, Lowe AJ, Perret J, Bui MQ, et al. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. The Lancet Respiratory medicine. 2018;6(7):535-44.

18. Karmaus W, Mukherjee N, Janjanam VD, Chen S, Zhang H, Roberts G, et al. Distinctive lung function trajectories from age 10 to 26 years in men and women and associated early life risk factors - a birth cohort study. Respiratory research. 2019;20(1):98.

19. Kerstjens HA, Rijcken B, Schouten JP, Postma DS. Decline of FEV1 by age and smoking status: facts, figures, and fallacies. Thorax. 1997;52(9):820-7.

20. Grol MH, Gerritsen J, Vonk JM, Schouten JP, Koeter GH, Rijcken B, et al. Risk factors for growth and decline of lung function in asthmatic individuals up to age 42 years. A 30-year follow-up study. American journal of respiratory and critical care medicine. 1999;160(6):1830-7.

21. James AL, Palmer LJ, Kicic E, Maxwell PS, Lagan SE, Ryan GF, et al. Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. American journal of respiratory and critical care medicine. 2005;171(2):109-14.

22. Aanerud M, Carsin AE, Sunyer J, Dratva J, Gislason T, Jarvis D, et al. Interaction between asthma and smoking increases the risk of adult airway obstruction. The European respiratory journal. 2015;45(3):635-43.

23. Aggarwal AN, Gupta D, Sharma CP, Jindal SK. Effect of household exposure to environmental tobacco smoke on airflow mechanics in asymptomatic healthy women. The Indian journal of medical research. 2004;119(1):18-23.

24. Tager IB, Segal MR, Speizer FE, Weiss ST. The natural history of forced expiratory volumes. Effect of cigarette smoking and respiratory symptoms. The American review of respiratory disease. 1988;138(4):837-49.

25. Sherrill DL, Lebowitz MD, Knudson RJ, Burrows B. Smoking and symptom effects on the curves of lung function growth and decline. The American review of respiratory disease. 1991;144(1):17-22.

26. Belgrave DCM, Granell R, Turner SW, Curtin JA, Buchan IE, Le Souef PN, et al. Lung function trajectories from pre-school age to adulthood and their associations with early life factors: a retrospective analysis of three population-based birth cohort studies. The Lancet Respiratory medicine. 2018;6(7):526-34.

27. Berry CE, Billheimer D, Jenkins IC, Lu ZJ, Stern DA, Gerald LB, et al. A Distinct Low Lung Function Trajectory from Childhood to the Fourth Decade of Life. American journal of respiratory and critical care medicine. 2016;194(5):607-12.

28. Swanney MP, Ruppel G, Enright PL, Pedersen OF, Crapo RO, Miller MR, et al. Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. Thorax. 2008;63(12):1046-51.