related to respiratory infections in infancy and to atopy. Incident wheeze from one to 7 years was strongly associated with atopy, while late-onset wheeze was related to rhino conjunctivitis, smoking and (marginally) body mass.

Conclusions Advances in the understanding and prevention of wheeze may be assisted by directing attention to maternal smoking, breastfeeding and respiratory infections in infancy, atopy in childhood, rhino conjunctivitis in adolescence, and smoking and perhaps obesity in adult life.

S113 THE EFFECT OF SMALL AIRWAY DISEASE AND EMPYSEMA ON THE ASSOCIATION BETWEEN SMOKING AND LUNG FUNCTION, AND BRONCHODILATOR RESPONSE

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Introduction and objectives The airflow limitation of COPD results from small airway disease and emphysema. These phenotypes are likely to have independent genetic risk factors. It is not known if the heterogeneity of COPD accounts for the relatively weak association between pack-years smoked and forced expiratory volume in 1 s (FEV1) seen within smoking populations, or bronchodilator response (BDR). This study aimed to assess the effect of these phenotypes on the association between smoking and FEV1 and on BDR.

Method The international COPD genetics network is a multi-centre study aimed at identifying genes that predispose to COPD, in which high resolution computed tomography (HRCT) was used to quantify components of the COPD phenotype: (i) emphysema detected by radiologists (RE), (ii) emphysema assessed as per cent low attenuation area (%LAA) and (iii) airway wall thickness (AWT) for small airways, and average per cent wall area (WA%). They were then assessed for their effect on the association between smoking and lung function (FEV1% predicted (FEV1%)), and on BDR.

Results RE data were available for 1159 individuals, 745 had complete data for Pi10, Pi20, AWT% and %LAA. The association between pack-years smoked and FEV1% was greater in those without (r²=0.41), compared to those with, RE (r²=0.12, p<0.001 for difference in effect). AWT and RE correlated with FEV1% but had different relationships with smoking: AWT was positively associated with pack-years but there was no relationship between RE severity and pack-years smoked. RE, %LAA and AWT made independent contributions to FEV1%. Post-bronchodilator increase in FEV1 was inversely associated with severity of RE (Abstract S113 Table 1), even after adjustment for pre-bronchodilator FEV1 (p<0.01). BDR was also inversely associated with %LAA (p=0.02, and p=0.05 adjusted for baseline FEV1).

Abstract S113 Table 1

<table>
<thead>
<tr>
<th>Severity of RE</th>
<th>Mild (5–25%)</th>
<th>Moderate (25–50%)</th>
<th>Severe (&gt;50%)</th>
<th>p (trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>228</td>
<td>185</td>
<td>266</td>
<td>—</td>
</tr>
<tr>
<td>BDR, FEV1 (mls)</td>
<td>171.3±188.2</td>
<td>134.4±174.7</td>
<td>100.2±129.6</td>
<td>≤0.0001</td>
</tr>
</tbody>
</table>

Abstract S113 Figure 1

Conclusions The AWT component of COPD, but not the severity of RE, increases with pack-years smoked, and the association between pack-years and FEV1% is greatest in those with an airway predominant phenotype. This suggests different gene-smoking interactions between phenotypes. RE and %LAA independently contribute to FEV1% and therefore measure different components of emphysema, however both were inversely associated with BDR.

S114 A DOUBLE BLIND, PLACEBO CONTROLLED, RANDOMISED, STUDY TO ASSESS THE EFFECTS OF PLACEBO, CODEINE AND TALNETANT, ON CITRIC ACID COUGH THRESHOLD IN HEALTHY SUBJECTS

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Background Previous studies have shown a reduction in cough response to inhaled citric acid after blocking NK1, NK2 and also NK3 receptors in guinea pigs. NK3 receptor may be more relevant to study the role of tachykinins in cough due to their greater specificity for its agonist neurokinin B. We studied a specific NK3 receptor antagonist Talnetant to determine the effect on the human cough reflex sensitivity to citric acid in healthy individuals. Oral codeine and placebo were included as comparators.

Methods Double-blind, randomised, placebo-controlled, 4-period cross-over study in non-smoking healthy adult volunteers. A total of 28 subjects (12M, 16F) with mean age of 33 years (SD 10.5, range 22–55) were studied. Each subject received A. matched placebos; B. Talnetant 200 mg; C. Talnetant 25 mg; D. Codeine 60 mg, in a double blind double dummy manner. Subjects were randomly assigned to one of four treatment sequences (ABCD, BCDA, DCAB, BDCA). Each study period was 24 h with citric-acid challenges performed at 2, 6, 10 and 24 h post dose and a 7 day washout period between treatments.

Results There was no significant difference in logCS Citric acid between Talnetant 25 mg, 200 mg and placebo at any time point (see Abstract S114 Figure 1). The ‘positive’ control codeine had a non-significant trend for improvement in logCS compared to placebo (all confidence intervals contained unity). Talnetant was adequately absorbed with sustained blood levels at time points designed to coincide with the cough challenges.

Abstract S114 Figure 1

Measurements in patients with chronic cough

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Page dimensions: 623.6x822.0

[Image 307x69 to 553x235]