Is Childhood Pneumonia Associated With Future Disease Susceptibility? An Investigation Into the Early Origins of Chronic Obstructive Pulmonary Disease

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PART 1:
Title: Childhood Pneumonia Increases Risk for Chronic Obstructive Pulmonary Disease

Short Title: Childhood Pneumonia Increases Risk for COPD

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Conflicts of Interest
Craig P. Hersh has received lecture fees from Novartis and consulting fees from CSL Behring. The remaining authors have no financial relationships relevant to this article to disclose.

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ABSTRACT

Background
Development of adult respiratory disease is influenced by events in childhood. The impact of childhood pneumonia on chronic obstructive pulmonary disease (COPD) is not well defined. We hypothesize that childhood pneumonia is a risk factor for reduced lung function and COPD in adult smokers.

Methods
COPD cases and control smokers between 45–80 years old from the US COPDGene Study were included. Childhood pneumonia was defined by self-report of pneumonia at <16 years. Subjects with lung disease other than COPD or asthma were excluded. Smokers with and without childhood pneumonia were compared on measures of respiratory disease, lung function, and quantitative analysis of chest CT scans.

Results
Of 10,192 adult smokers, 854 (8.4%) reported pneumonia in childhood. Childhood pneumonia was associated with COPD (OR 1.40; 95%CI 1.17-1.66), chronic bronchitis, increased COPD exacerbations, and lower lung function: post-bronchodilator FEV₁ (69.1 vs. 77.1% predicted), FVC (82.7 vs. 87.4% predicted), FEV₁/FVC ratio (0.63 vs. 0.67; p<0.001 for all comparisons). Childhood pneumonia was associated with increased airway wall thickness on CT, without significant difference in emphysema. Having both pneumonia and asthma in childhood further increased the risk of developing COPD (OR 1.85; 95%CI 1.10-3.18).

Conclusions
Children with pneumonia are at increased risk of future smoking-related lung disease including COPD and decreased lung function. This association is supported by airway changes on chest CT scans. Childhood pneumonia may be an important factor in the early origins of COPD, and the combination of pneumonia and asthma in childhood may pose the greatest risk.

CLINICAL TRIAL REGISTRATION
ClinicalTrials.gov, NCT00608764 (Active since January 28, 2008)
https://clinicaltrials.gov/ct2/show/NCT00608764
INTRODUCTION

Pneumonia is a common pediatric diagnosis that poses a significant risk for future respiratory disease.[1, 2] Multiple investigations have found an association between pneumonia in childhood and decreased adult lung function, raising the question of whether childhood pneumonia is a risk factor for chronic obstructive pulmonary disease (COPD). Prior studies are limited by small sample sizes, short-term follow-up, absence of post-bronchodilator lung function, differing definitions of respiratory illness, sampling bias, and recall bias.[3-10] This study examines the effect of childhood pneumonia in a large population of older adults, including objective diagnosis of COPD with standardized post-bronchodilator spirometry and analysis of chest computed tomography (CT).

Smoking remains a major risk for children, with one in fifteen high school seniors reporting daily cigarette use.[11] Most smokers initiate the habit by age 18, putting them at risk for a wide range of comorbidities including COPD.[12] Recently, there has been interest in the early origins of COPD and the potential synergistic relationship between childhood respiratory infection, aberrant lung development, and increased susceptibility to smoking related injury.[10, 13-15] More data is needed to guide providers in anticipating the outcomes of childhood pneumonia and potential additional complications from smoking.

This study examines the association between pneumonia in childhood and future respiratory illness in smokers. We hypothesize that childhood pneumonia is a risk factor for reduced lung function and COPD in adult smokers.
METHODS

Subjects
We evaluated 10,192 current and former United States smokers with and without COPD from the COPDGene Study, a multicenter, observational study designed to identify genetic and environmental factors associated with COPD. COPDGene enrolled subjects from 2008–2011. It was approved by the Institutional Review Boards at each of the twenty-one clinical sites. All participants provided written informed consent (e-Appendix 1).[16] Subjects were 45–80 years of age, Non-Hispanic White or African American, and had at least a 10 pack-year smoking history. Exclusion criteria included history of lung disease other than COPD or asthma. Study protocol, enrollment criteria, and data collection forms were previously described and are available at www.copdgene.org.[16, 17]

Data Collection
Participants completed a modified American Thoracic Society Respiratory Epidemiology Questionnaire, Modified Medical Research Council (MMRC) dyspnea scale, and questionnaires related to demographics and medical history.[17-19] Quality of life was assessed using, with permission, the St. George's Respiratory Questionnaire (SGRQ).[20] Subjects completed a standardized spirometry protocol (ndd EasyOne Spirometer, Zurich, Switzerland). Inspiratory and expiratory chest CT scans were obtained. Airway measurements, performed using VIDA software (VIDA Diagnostics; Iowa City, Iowa), assessed wall thickening in segmental airways, subsegmental airways, and the square root of the wall area of a hypothetical airway with 10mm internal perimeter (SRWA-Pi10).[21, 22] SLICER software (www.slicer.org) was used to
quantify emphysema by inspiratory scan low-attenuation areas < -950 Hounsfield units (HU) and gas trapping on expiratory scan at < -856 HU.[23]

**Case Identification**

Childhood pneumonia was defined by subject self-report. The questionnaire asked: “Have you ever had pneumonia or bronchopneumonia?” and their age at the first episode. Subjects were classified as childhood pneumonia if they reported an age of first pneumonia at < 16 years or “As a child; age not known.” Subjects were classified as no childhood pneumonia if they reported no pneumonias, an age of first pneumonia ≥ 16 years, or if they did not indicated their first pneumonia was during childhood. Age sixteen was used to define pediatric pneumonia as this was when most subjects in the cohort started smoking (mean 16.9, standard deviation 4.6 years), which is concurrent with a rise in subjects reporting a first episode of pneumonia between ages 15-20.

Chronic bronchitis was defined by cough and phlegm production lasting more than three months per year for at least two years. COPD exacerbations were defined by use of antibiotics or systemic steroids. Severe COPD exacerbations required an emergency room visit or hospitalization. Childhood asthma was defined as reported history of asthma diagnosed by a health professional with age of onset at < 16. COPD was defined based on post-bronchodilator forced expiratory volume in the first second (FEV₁) to forced vital capacity (FVC) ratio < 0.7 with FEV₁ < 80% predicted, corresponding to Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stages 2-4.[24] Control smokers had normal spirometry, defined as FEV₁/FVC ≥ 0.7 and FEV₁ ≥ 80%.
Statistical Analysis

Subjects with and without childhood pneumonia were compared by demographics, respiratory symptoms/diseases, lung function, and CT measurements. Statistical analysis was performed using R v3.1.1. Single variable analysis used chi-square tests, t-tests, or Wilcoxon rank sum tests. Multivariable regression analysis was performed, with most models adjusted for standard covariates of age, gender, race and smoking history. Additional covariates of FEV₁% predicted, height, body mass index, and CT scanner model were included for some analyses. Logistic regression reported odds ratios (OR) with 95% confidence intervals (CI) and linear regression reported absolute differences (β) with standard errors (SE). Subjects with missing or unclassifiable responses were removed from specific analyses.

Regression analysis was repeated in three subsets. First, to assess the effect of asthma, the analysis was performed on subjects without childhood asthma. Second, the analysis was run on only subjects with childhood asthma. Finally, to assess the effect of recall bias, spirometry was analyzed in subjects who did not report a history of COPD or emphysema.

RESULTS

Subject Classification and Characteristics

COPDGene includes 10,192 current and former smokers (e-Figure 1). Thirty-six subjects were excluded, as it was not possible to classify their pneumonia history by questionnaire response. Of the 10,156 subjects included, 854 (8.4%) reported childhood pneumonia. Of these, 405 subjects had COPD and 282 had normal spirometry. Of the 9,302 subjects without childhood pneumonia,
3,267 had COPD, and 4,097 had normal spirometry. Subjects with GOLD Stage 1 spirometry (FEV\textsubscript{1}/FVC<0.7 with FEV\textsubscript{1}≥80% predicted) or subjects with Preserved Ratio Impaired Spirometry (PRISm, FEV\textsubscript{1}/FVC≥0.7 with FEV\textsubscript{1}<80% predicted) were not included in COPD analysis; they were included in the other assessments.[25]

Subjects with childhood pneumonia were older and more likely to be non-Hispanic white (Table 1). They were more likely to report living with a smoker in childhood, having a greater lifetime smoking intensity, were less likely to be current smokers, and had an increased number of lifetime pneumonia episodes. The distribution of age of first pneumonia can be seen in e-Figure 2.

**Respiratory Symptoms and Disease**

Smokers with childhood pneumonia were more likely to develop COPD (Table 2). This remained robust when childhood asthma was added to the model. Childhood pneumonia was associated with increased chronic bronchitis, as well as more frequent and severe COPD exacerbations in the year prior (Table 3). They were more likely to report asthma diagnosed by a healthcare provider and onset in childhood. Childhood pneumonia was associated with worse disease-related quality of life with higher SGRQ, and more severe dyspnea with higher MMRC.

Spirometry showed post-bronchodilator FEV\textsubscript{1} % predicted, FVC% predicted and FEV\textsubscript{1}/FVC were all significantly lower in subjects with childhood pneumonia (Figure 1, Table 4). In regression analysis, chest CT parameters related to airways disease were significantly increased in subjects with childhood pneumonia, with greater airway wall thickness in segmental and
subsegmental airways and greater SRWA-Pi10 (Figure 2, Table 5, e-Table 1). These subjects also had increased gas trapping. Multivariable analysis showed no difference in emphysema or total lung capacity measured by chest CT.

**Sensitivity and Recall Analyses**

To assess the effect of asthma, regression analysis was repeated in a subset of 9,405 subjects, excluding 723 with childhood asthma and 28 with unclassifiable childhood asthma status (e-Table 2). Childhood pneumonia remained significantly associated with COPD (OR1.24; 95%CI 1.03-1.50). Other significant associations with childhood pneumonia were maintained, with the exception of the association with severe COPD exacerbations in the past year, which was attenuated.

A corresponding analysis was run including only 723 subjects with childhood asthma (e-Table 3). In this subset, having childhood pneumonia showed a stronger association with COPD than in the cohort overall (OR1.85; 95%CI 1.10-3.18). The associations with post-bronchodilator percent predicted FEV$_1$ and FVC remained significant. Other associations were no longer significant.

To assess recall bias, the regression analysis was repeated in a subset of 5,743 who did not report COPD or emphysema diagnosis at enrollment (e-Table 4). This included subjects with undiagnosed COPD and without COPD. Although prevalence of COPD was not significantly increased in this subset, both percent predicted FEV$_1$ and FVC remained significantly lower in subjects with childhood pneumonia.
DISCUSSION

In adult smokers, a history of childhood pneumonia was associated with COPD and reduced lung function, with the greatest association in the subset of subjects with both pneumonia and asthma in childhood. Those with childhood pneumonia had increased chronic bronchitis, more frequent and severe COPD exacerbations, increased dyspnea, and worse disease-related quality of life. There was a novel finding of greater airways disease present in chest CT scans of subjects with childhood pneumonia, supporting the idea that childhood disease is associated with long term structural differences in the lung and a distinct COPD phenotype. By comparison, there was no difference in emphysema.

The role of childhood pneumonia in COPD development has been investigated for over sixty years. Oswald surveyed 1000 adults with chronic bronchitis in London from 1951-53, finding 14.3% reported childhood pneumonia compared to 6% of controls.[26] In the 1970’s Burrows proposed that childhood respiratory infections are a risk factor for obstructive lung disease in adults, with an enhanced effect in smokers, based on decreased FEV$_1$ and FEV$_1$/FVC and increased chronic bronchitis in 415 subjects, mean age of 44.5, who reported childhood respiratory trouble at <16 years.[3] Four subsequent investigations looked more closely at the relationship between childhood pneumonia in British subjects born between 1911-1935 and adult lung function at ages 34–74, each independently finding an association with decreased FEV$_1$ and FVC, and suggesting an association between childhood pneumonia and COPD.[4-7] Only one of these five studies used post-bronchodilator data and none included COPD diagnosis in their outcomes.[7]
The European Community Respiratory Health Survey assessed pre-bronchodilator lung function in subjects ages 20-44 in 1991-93 and then again 5-11 years later, showing risk of developing COPD was doubled in subjects with self-reported history of serious respiratory infection at <5 years, and that this factor accounted for about 8% of new cases.[8, 9, 13] Recent data from the Tucson Children’s Respiratory Study provided longitudinal post-bronchodilator lung function in 44 subjects born between 1980-84 with radiographically diagnosed pneumonia at ≤3 years, demonstrating an association with a persistent decrease in post-bronchodilator FEV$_1$ and FEV1/FVC up to age 26.[10]

Compared to prior investigations, our study examines 10,156 United States smokers ages 45-80, including 854 subjects with childhood pneumonia. Our analysis supports the association between childhood pneumonia, reduced lung function in adulthood, and COPD. Our study is unique due to the older age of participants, the objective diagnosis of COPD by post-bronchodilator spirometry, and chest CT analysis. Additionally, few other studies have addressed this question in a population of this size and included assessment of the combined effect of pneumonia and childhood asthma.

Research into the association between childhood and adult respiratory disease is complicated by the inherent difficulty differentiating between diagnoses of childhood pneumonia, asthma, and other respiratory illnesses, which can overlap and evolve over time. Asthma is independently associated with both childhood pneumonia and adult COPD.[10, 13, 27, 28] More recent studies of long-term outcomes from childhood pneumonia have differentiated pneumonia from other respiratory illness and have accounted for asthma in their analyses, finding that the effect of
childhood pneumonia on future lung function is greater than that of other childhood respiratory infections, and is robust to adjustments for childhood asthma.[5-8, 10] This is similar to our finding, where the association of childhood pneumonia with COPD persisted even after adjusting for or removing childhood asthmatics. Notably, we found that it was the combined effect of pneumonia and asthma in childhood had the greatest association with COPD.

Prior investigators have cited the possibility of impaired childhood lung growth and development playing a role in this association.[2, 4-6] Chest CT changes demonstrated in this analysis, with increased airways disease in subjects with childhood pneumonia, supports this hypothesis. There are two potential explanations. The first is that childhood pneumonia may cause airways changes that increased risk for future disease. Alternatively, there may be an underlying developmental abnormality of the lung that increases risk for both childhood pneumonia and lung disease in adult smokers. While asthma has also been associated with airways disease on CT scans, the imaging associations in this analysis were maintained even in a subset analysis where childhood asthmatics were removed, suggesting that childhood pneumonia likely has an independent role.[29]

**Limitations**

The ideal study for examining the connection between childhood pneumonia and COPD would follow subjects from conception to death.[30] However, the challenges of such a study have forced researchers to take other approaches. Studies that use historical medical records paired with current cohorts available for lung function testing can be limited by selection bias.[4-7] Studies that follow childhood cohorts are limited by younger age at follow-up, especially given
that the highest rates of COPD are in those over 65.[7, 10, 31] An alternative method, employed by our study, was the collection of self-reported medical history from a cohort of adults, understanding that this does not include details such as gestational age, birth weight and childhood socio-economic status. This COPDGene Study assessment includes only smokers; therefore we could not address the effect of childhood pneumonia in non-smokers.

We acknowledge that our strategy may lead to potential recall bias, where adult subjects with respiratory disease may be more likely to recall childhood illness. This analysis included a separate assessment for recall bias, focusing only on subjects who did not report a known COPD diagnosis, and thus were less likely to be biased in recalling childhood respiratory problems. In this subset analysis, childhood pneumonia remained associated with reduced lung function. Therefore, it is unlikely that overall study results were influenced by recall bias. Childhood pneumonia was not associated with COPD in this analysis, though this is not surprising given that the subset includes nearly all those with normal lung function, while being most likely to remove subjects with more severe COPD.

Self-reported pneumonia is a potential source of misclassification, however, prior studies have shown that self-reported pneumonia diagnosis has relatively good agreement with the medical record.[32] Additionally, versions of the American Thoracic Society Questionnaire have previously been used to examine pneumonia history, and prior epidemiologic surveys examining the relationship have also used subject self-report.[3, 9, 33, 34]
CONCLUSIONS

We found that the combination of pneumonia in childhood and smoking in adulthood is associated with COPD, increased respiratory symptoms, and reduced lung function. This was supported by novel findings of airways disease on chest CT scans. The greatest association with COPD was seen in those who had both pneumonia and asthma in childhood. Further research will be required to identify whether there are genetic associations that may play a role in determining a subtype of COPD that originates with childhood respiratory disease. In the meantime, medical providers have a valuable opportunity to reduce childhood pneumonias, especially among asthmatics, and to counsel patients about the increased risk from smoke exposure in those who have had pneumonia during childhood.
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Guarantor Statement
Craig P. Hersh takes responsibility for the content of the manuscript, including the data and analysis.

Author Contributions
Lystra P. Hayden contributed to the conception and design of the work, analysis and interpretation of data, drafting of the work, revising it critically for important intellectual content, and providing final approval of the published version.

Brian D. Hobbs, Robyn T. Cohen and William Checkley, contributed to the analysis and interpretation of data, revising the work critically for important intellectual content, and providing final approval of the published version.

James D. Crapo and Robert A. Wise contributed to the acquisition of data, revising the work critically for important intellectual content, and providing final approval of the published version.

Craig P. Hersh contributed to the conception and design of the work, the acquisition of data, analysis and interpretation of data, drafting of the work, revising it critically for important intellectual content, and providing final approval of the published version.

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial Disclosures
Craig P. Hersh has received lecture fees from Novartis and consulting fees from CSL Behring. The remaining authors have no financial relationships relevant to this article to disclose.

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Neither the NIH nor the COPD Foundation Industry Advisory Board had a role in the study design, collection, analysis and interpretation of the data, writing of the report or the decision to submit the paper for publication.

Other Contributions
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**PFT QA Core, LDS Hospital, Salt Lake City, UT:** Robert Jensen, PhD.

**Data Coordinating Center and Biostatistics, National Jewish Health, Denver, CO:** Douglas Everett, PhD, Anna Faino, MS, Ruthie Knowles, Joe Piccoli, Matt Strand, PhD, Carla Wilson, MS.

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17 COPDGene. Copdgene, phase i study documents, accessed 3/13/15


### Table 1: Characteristics of Subjects With and Without History of Childhood Pneumonia

<table>
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<tr>
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<th>Childhood Pneumonia</th>
<th>No Childhood Pneumonia</th>
<th>p Value b</th>
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<tr>
<td></td>
<td>N = 854 (8.4%)</td>
<td>N = 9302 (91.6%)</td>
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<td><strong>DEMOGRAPHIC</strong></td>
<td></td>
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<tr>
<td>Male gender (%)</td>
<td>437 (51.2%)</td>
<td>4990 (53.6%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>61.7 (8.9)</td>
<td>59.4 (9.0)</td>
<td>&lt;0.001 c</td>
</tr>
<tr>
<td>Non-Hispanic white (%)</td>
<td>693 (81.1%)</td>
<td>6073 (65.3%)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>SMOKE EXPOSURE</strong></td>
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<tr>
<td>In-utero smoke exposure (%) a</td>
<td>206 (33.0%)</td>
<td>2082 (30.2%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Lived with smoker in childhood (%) a</td>
<td>732 (85.7%)</td>
<td>7618 (81.9%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Mean age started smoking, years (SD)</td>
<td>16.5 (4.4)</td>
<td>16.9 (4.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Pack-years of smoking (SD)</td>
<td>49.8 (28.4)</td>
<td>43.7 (24.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>379 (44.4%)</td>
<td>5011 (53.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PNEUMONIA HISTORY</strong></td>
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<tr>
<td>Ever had pneumonia (%)</td>
<td>854 (100.0%)</td>
<td>2979 (33.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnosed with pneumonia by healthcare provider (%) a</td>
<td>821 (96.1%)</td>
<td>2920 (31.4%)</td>
<td>&lt;0.001</td>
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<tr>
<td>Pneumonia childhood age unknown (%)</td>
<td>378 (44.3%)</td>
<td>0 (0.0%)</td>
<td>&lt;0.001</td>
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<tr>
<td>Age first pneumonia in years, mean (SD) a</td>
<td>7.7 (4.5)</td>
<td>42.5 (15.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lifetime pneumonia episodes (SD) a</td>
<td>3.9 (4.9)</td>
<td>2.5 (3.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: SD = standard deviation.

a Subjects included are fewer than total subjects due to subject survey response being missing or unclassifiable.

b Univariate analysis with chi-square or Wilcoxon rank sum test unless otherwise specified. c t test.
### Table 2: COPD in Subjects With and Without History of Childhood Pneumonia

<table>
<thead>
<tr>
<th>COPD</th>
<th>Childhood Pneumonia</th>
<th>No Childhood Pneumonia</th>
<th>Impact of Childhood Pneumonia</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 687 (8.5%)</td>
<td>N = 7364 (91.5%)</td>
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<tr>
<td>COPD, GOLD 2-4</td>
<td>405 (59.0%)</td>
<td>3267 (44.4%)</td>
<td>1.40 (1.17, 1.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD, GOLD 2-4 adjusted for childhood asthma</td>
<td></td>
<td></td>
<td>1.30 (1.09, 1.55)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Abbreviations: COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

* Each row represents a separate regression model. Odds ratio (OR) and 95% confidence interval (CI) for logistic regression.
* Covariates for all analyses = age at enrollment in years + gender + race + pack years.

### Table 3: Respiratory Symptoms and Disease in Subjects With and Without History of Childhood Pneumonia

<table>
<thead>
<tr>
<th>Respiratory Symptoms and Disease</th>
<th>Childhood Pneumonia</th>
<th>No Childhood Pneumonia</th>
<th>Impact of Childhood Pneumonia</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 854 (8.4%)</td>
<td>N = 9302 (91.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic bronchitis (%)</td>
<td>214 (25.1%)</td>
<td>1730 (18.6%)</td>
<td>1.40 (1.18, 1.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of COPD exacerbations in past year (SD)</td>
<td>0.65 (1.2)</td>
<td>0.36 (0.9)</td>
<td>0.18 (0.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Had a severe COPD exacerbation in past year (%)</td>
<td>140 (16.4%)</td>
<td>1063 (11.4%)</td>
<td>1.28 (1.04, 1.58)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diagnosed with asthma by healthcare provider (%)</td>
<td>239 (28.0%)</td>
<td>1508 (16.3%)</td>
<td>2.15 (1.83, 2.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Childhood asthma (%)</td>
<td>137 (16.0%)</td>
<td>586 (6.3%)</td>
<td>3.30 (2.68, 4.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGRQ Score, Total (SD)</td>
<td>32.4 (24.0)</td>
<td>26.9 (22.8)</td>
<td>2.32 (0.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMRC Dyspnea Scale, 0-4 (SD)</td>
<td>1.6 (1.5)</td>
<td>1.3 (1.4)</td>
<td>0.12 (0.04)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Abbreviations: COPD = chronic obstructive pulmonary disease; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire; MMRC = Modified Medical Research Council.

* Subjects included are fewer than total subjects due to subject survey response being missing or unclassifiable.
* Each row represents a separate regression model.
* Odds ratio (OR), 95% confidence interval (CI) for logistic regression; beta coefficient (β), standard error (SE) for linear regression.
* Covariates for all analyses = age at enrollment in years + gender + race + pack-years. Additional covariates: current smoker; current smoker & FEV₁ % predicted; FEV₁ % predicted.
### Table 4: Effect of Childhood Pneumonia on Lung Function

<table>
<thead>
<tr>
<th>Spirometry</th>
<th>Childhood Pneumonia</th>
<th>No Childhood Pneumonia</th>
<th>Impact of Childhood Pneumonia</th>
<th>β</th>
<th>SE</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 850 (8.4%)</td>
<td>N = 9245 (91.6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ post-BD % predicted (SD)</td>
<td>69.1% (25.7)</td>
<td>77.1% (25.4)</td>
<td>-6.22 (0.88)</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC post-BD % predicted (SD)</td>
<td>82.7% (18.6)</td>
<td>87.4% (18.3)</td>
<td>-3.89 (0.65)</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁/FVC post-BD (SD)</td>
<td>0.63 (0.17)</td>
<td>0.67 (0.16)</td>
<td>-0.02 (0.005)</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FEV₁ = forced expiratory volume in the first second; FVC = forced vital capacity; post-BD = post bronchodilator.  

a Each row represents a separate regression model. Beta coefficient (β) and standard error (SE) for linear regression.  
b Covariate used for all analyses = pack years.  
c Additional covariates = age at enrollment + gender + race + height.

### Table 5: Effect of Childhood Pneumonia on Chest CT Parameters

<table>
<thead>
<tr>
<th>Chest CT Parameters</th>
<th>Impact of Childhood Pneumonia</th>
<th>β</th>
<th>SE</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wall Area %, Segmental</td>
<td>0.46 (0.12)</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wall Area %, Subsegmental</td>
<td>0.47 (0.16)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRWA-Pi10</td>
<td>0.02 (0.005)</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emphysema % (-950 HU)</td>
<td>0.18 (0.32)</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gas Trapping %, expiratory scan (-856HU)</td>
<td>1.97 (0.72)</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Lung Capacity (L)</td>
<td>0.001 (0.04)</td>
<td>0.99</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CT = computed tomography; HU = Hounsfield units; SRWA-Pi10 = square root wall area of a hypothetical airway with 10mm internal perimeter.  
a Data only available for a limited portion of the cohort.  
b Each row represents a separate regression model.  
c Beta coefficient (β) and standard error (SE) for linear regression.  
d Covariates used = age at enrollment in years + gender + race + pack-years + body mass index + CT scanner model.
FIGURES

**Figure 1** Decreased lung function with history of childhood pneumonia. Post-bronchodilator spirometry values are shown.

Abbreviations: FEV$_1$ = forced expiratory volume in the first second; FVC = forced vital capacity.

**Figure 2** Airway changes on chest CT scans are associated with childhood pneumonia.
SUPPLEMENT

e-Figure 1: Subject Classification

e-Figure 1 Classification of subjects in cohort based on childhood pneumonia status.  
*Includes subjects with GOLD Stage 1 (FEV₁/FVC < 0.7 with FEV₁ ≥ 80% predicted) or Preserved Ratio Impaired Spirometry (PRISm, FEV₁/FVC ≥ 0.7 with FEV₁ < 80% predicted).
e-Figure 2: Pneumonia Age Distribution

(a) Age at First Pneumonia: All Smokers
(N = 3443)

(b) Age at First Pneumonia: Childhood Pneumonia
(N = 493)

(c) Age at First Pneumonia: No Childhood Pneumonia
(N = 2950)

The e-Figure 2 shows the distribution of age of first pneumonia in entire cohort (a), in subjects with a history of childhood pneumonia (b), and in subjects without a history of childhood pneumonia (c). It includes all subjects who reported an age of first pneumonia.
<table>
<thead>
<tr>
<th>Chest CT Parameters</th>
<th>Childhood Pneumonia</th>
<th></th>
<th>No Childhood Pneumonia</th>
<th></th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>SD</td>
<td>N</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Wall Area %, Segmental</td>
<td>792</td>
<td>61.9% (3.3)</td>
<td>8693</td>
<td>61.4% (3.3)</td>
<td>&lt;0.001 a</td>
</tr>
<tr>
<td>Wall Area %, Subsegmental</td>
<td>286</td>
<td>64.8% (2.6)</td>
<td>2923</td>
<td>64.3% (2.6)</td>
<td>0.003 a</td>
</tr>
<tr>
<td>SRWA-Pi10</td>
<td>768</td>
<td>3.70 (0.14)</td>
<td>8526</td>
<td>3.68 (0.13)</td>
<td>0.01 b</td>
</tr>
<tr>
<td>Emphysema % (-950 HU)</td>
<td>789</td>
<td>7.2% (9.7)</td>
<td>8679</td>
<td>6.1% (9.6)</td>
<td>&lt;0.001 b</td>
</tr>
<tr>
<td>Gas Trapping %, expiratory scan (-856HU)</td>
<td>609</td>
<td>27.0% (21.4)</td>
<td>6810</td>
<td>22.1% (20.3)</td>
<td>&lt;0.001 b</td>
</tr>
<tr>
<td>Total Lung Capacity (L)</td>
<td>789</td>
<td>5.7 (1.4)</td>
<td>8679</td>
<td>5.5 (1.4)</td>
<td>0.004 a</td>
</tr>
</tbody>
</table>

Abbreviations: CT = computed tomography; HU = Hounsfield units. SRWA-Pi10 = square root wall area of a hypothetical airway with 10mm internal perimeter.

Univariate analysis with: a t-test; b Wilcoxon rank sum test.
Table 2: Effect of Childhood Pneumonia with Childhood Asthmatics Removed

<table>
<thead>
<tr>
<th>Outcomes in N = 9,405 subjects, after removal of childhood asthmatics</th>
<th>Impact of Childhood Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood pneumonia N = 717 (7.6%); No childhood pneumonia N = 8688 (92.4%)</td>
<td>OR (95% CI) or β (SE)</td>
</tr>
<tr>
<td><strong>RESPIRATORY SYMPTOMS AND DISEASE</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>1.34</td>
</tr>
<tr>
<td>COPD, GOLD 2-4</td>
<td>1.24</td>
</tr>
<tr>
<td>Had a severe COPD exacerbation in past year</td>
<td>1.20</td>
</tr>
<tr>
<td>Number of COPD exacerbations in past year</td>
<td>0.16</td>
</tr>
<tr>
<td>SGRQ Score, Total a</td>
<td>2.00</td>
</tr>
<tr>
<td>MMRC Dyspnea Scale (0-4) a</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>LUNG FUNCTION</strong></td>
<td></td>
</tr>
<tr>
<td>FEV₁ post-BD (% predicted) a</td>
<td>-5.52</td>
</tr>
<tr>
<td>FVC post-BD (% predicted) a</td>
<td>-3.31</td>
</tr>
<tr>
<td>FEV₁/FVC post-BD (ratio x 100) a</td>
<td>-1.70</td>
</tr>
<tr>
<td><strong>CHEST CT PARAMETERS</strong></td>
<td></td>
</tr>
<tr>
<td>Wall Area %, Segmental a</td>
<td>0.31</td>
</tr>
<tr>
<td>Wall Area %, Subsegmental a</td>
<td>0.41</td>
</tr>
<tr>
<td>SRWA-Pi10 a</td>
<td>0.01</td>
</tr>
<tr>
<td>Emphysema % (-950 HU) a</td>
<td>0.14</td>
</tr>
<tr>
<td>Gas Trapping %, expiratory scan (-856HU) a</td>
<td>1.79</td>
</tr>
<tr>
<td>Total Lung Capacity (L) a</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Abbreviations: COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; SGRQ = St. George's Respiratory Questionnaire; MMRC = Modified Medical Research Council; FEV₁ = forced expiratory volume in the first second; FVC = forced vital capacity; post-BD = post bronchodilator; CT = computed tomography; HU = Hounsfield units. SRWA-Pi10 = square root wall area of a hypothetical airway with 10mm internal perimeter.

* From original 10,156 subjects, 723 were removed with childhood asthma and 28 were removed for unclassifiable asthma status.

a Subjects included are fewer than total subjects due to subject survey response being missing or unclassifiable. Each row represents a separate regression model. Included subjects in each model are those with classifiable data for the parameter.

c Odds ratio (OR), 95% confidence interval (CI) for logistic regression; beta coefficient (β), standard error (SE) for linear regression.

d Covariates for analysis = age at enrollment in years + gender + race + pack-years. Only covariate is pack-years.

Additional covariates:  
1 current smoker; 2 current smoker + FEV₁ % predicted; 3 FEV₁ % predicted; 4 height; 5 body mass index + CT scanner model.
### Table 3: Effect of Childhood Pneumonia in Childhood Asthmatics Only

**Outcomes in N = 723 subjects, only those with childhood asthma**

Childhood pneumonia N = 137 (18.9%); No childhood pneumonia N = 586 (81.1%)

<table>
<thead>
<tr>
<th>RESPIRATORY SYMPTOMS AND DISEASE</th>
<th>Impact of Childhood Pneumonia</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI) or β (SE)</td>
<td></td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>1.14 (0.13, 3.56)</td>
<td>0.56</td>
</tr>
<tr>
<td>COPD, GOLD 2-4</td>
<td>1.85 (1.10, 3.18)</td>
<td>0.02</td>
</tr>
<tr>
<td>Number of COPD exacerbations in past year</td>
<td>0.05 (0.12)</td>
<td>0.70</td>
</tr>
<tr>
<td>Had a severe COPD exacerbation in past year</td>
<td>1.22 (0.76, 1.94)</td>
<td>0.41</td>
</tr>
<tr>
<td>SGRQ Score, Total a</td>
<td>0.44 (2.02)</td>
<td>0.83</td>
</tr>
<tr>
<td>MMRC Dyspnea Scale (0-4) a</td>
<td>-0.12 (0.13)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

| LUNG FUNCTION                     |                                |         |
|-----------------------------------|                                |         |
| FEV₁ post-BD (% predicted) a       | -6.24 (2.35)                   | 0.008   |
| FVC post-BD (% predicted) a        | -4.66 (1.79)                   | 0.009   |
| FEV₁/FVC post-BD (ratio x 100) a  | -0.01 (0.01)                   | 0.64    |

| CHEST CT PARAMETERS               |                                |         |
|-----------------------------------|                                |         |
| Wall Area %, Segmental a          | 0.39 0.33                      | 0.25    |
| Wall Area %, Subsegmental a       | 0.32 0.48                      | 0.51    |
| SRWA-Pi10 a                       | 0.02 0.02                      | 0.27    |
| Emphysema % (-950 HU) a           | 0.42 0.77                      | 0.58    |
| Gas Trapping %, expiratory scan (-856HU) a | 0.76 1.93 | 0.70 |
| Total Lung Capacity (L) a         | -0.08 0.01                     | 0.43    |

Abbreviations: COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; SGRQ = St. George's Respiratory Questionnaire; MMRC = Modified Medical Research Council; FEV₁ = forced expiratory volume in the first second; FVC = forced vital capacity; post-BD = post bronchodilator; CT = computed tomography; HU = hounsfield units. SRWA-Pi10 = square root wall area of a hypothetical airway with 10mm internal perimeter.

- Subjects included are fewer than total subjects due to subject survey response being missing or unclassifiable.
- Each row represents a separate regression model. Included subjects in each model are those with classifiable data for the parameter.
- Odds ratio (OR), 95% confidence interval (CI) for logistic regression; beta coefficient (β), standard error (SE) for linear regression.
- Covariates for analysis = age at enrollment in years + gender + race + pack-years. Only covariate is pack-years.
- Additional covariates: current smoker; current smoker + FEV₁ % predicted; FEV₁ % predicted; height; body mass index + CT scanner model.
### Table 4: Recall Assessment in Subjects Who Did Not Report Known COPD or Emphysema Diagnosis

<table>
<thead>
<tr>
<th>Impact of Childhood Pneumonia&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Childhood Pneumonia&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No Childhood Pneumonia&lt;sup&gt;a&lt;/sup&gt;</th>
<th>OR&lt;sup&gt;b&lt;/sup&gt; (95% CI) or β (SE)</th>
<th>p Value&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD, GOLD 2-4 (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>54 (14.4%)</td>
<td>698 (13.0%)</td>
<td>1.03 (0.74, 1.41)</td>
<td>0.85&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; post-BD % predicted&lt;sup&gt;a&lt;/sup&gt;</td>
<td>87%</td>
<td>89%</td>
<td>-2.29 (0.91)</td>
<td>0.01</td>
</tr>
<tr>
<td>FVC post-BD % predicted&lt;sup&gt;a&lt;/sup&gt;</td>
<td>91%</td>
<td>93%</td>
<td>-1.80 (0.82)</td>
<td>0.03</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC post-BD (ratio x 100)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.74</td>
<td>0.75</td>
<td>-0.004 (0.005)</td>
<td>0.35&lt;sup&gt;d,e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; FEV<sub>1</sub> = forced expiratory volume in the first second; FVC = forced vital capacity; post-BD = post bronchodilator.

<sup>a</sup> Subjects included are fewer than total subjects due to subject survey response being missing or unclassifiable.

<sup>b</sup> Each row represents a separate regression model. Beta coefficient (β) and standard error (SE) for linear regression.

<sup>c</sup> Covariate used for all analyses is pack years. <sup>d</sup> Additional covariates: gender + age at enrollment + race; <sup>e</sup> + height.
PART II:
Susceptibility to Childhood Pneumonia: A Genome Wide Analysis

Lystra P. Hayden, MD,1,2 Michael H. Cho, MD, MPH,2,3 Merry-Lynn McDonald, PhD,2 James D. Crapo, MD,4 Terri H. Beaty, PhD,5 C.P. Hersh, MD, MPH,2,3 on behalf of the COPDGene Investigators.

1 Division of Respiratory Diseases, Boston Children's Hospital, 2 Channing Division of Network Medicine, Brigham and Women's Hospital, 3 Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, 4 National Jewish Health, 5 Bloomberg School of Public Health, Johns Hopkins University.

CLINICAL TRIAL REGISTRATION: NCT00608764 (Active since January 28, 2008)

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Neither the NIH nor the Industry Advisory Board had a role in the study design, collection, analysis and interpretation of the data, writing of the report or the decision to submit the paper for publication.

COMPETING INTERESTS
Craig P. Hersh has received lecture fees from Novartis and consulting fees from CSL Behring. The remaining authors have no financial relationships relevant to this article to disclose.
ABSTRACT

RATIONALE
Prior studies have indicated that pneumonia in childhood is associated with chronic obstructive pulmonary disease (COPD), reduced lung function, and airway disease on chest CT. The variability in prevalence of childhood pneumonia and the association with increased risk for COPD, suggests an underlying genetic susceptibility. There have been few prior investigations using genome wide association studies (GWAS) to investigate genetic predisposition for pneumonia.

This study aims to identify genetic variants involved in development of pneumonia.

METHODS
Phenotypic data was analyzed from current and former smokers with and without COPD participating in COPDGene, a multicenter observational study designed to identify genetic and environmental factors associated with COPD. Pneumonia was defined by subject self-report, with childhood pneumonia categorized as having the first episode at <16 years.

Childhood pneumonia GWAS were performed separately in non-Hispanic whites (NHW cases=685, controls=5967) and African-Americans (AA cases=158, controls=3124); results were combined in meta-analysis. Lifetime pneumonia GWAS were performed separately in NHWs (cases=2284, controls=3422) and AAs (cases=882, controls=2237); results were combined in meta-analysis. Top variants were assessed for shared genetic factors.

RESULTS
Meta-analysis of NHW and AA results from childhood pneumonia identified variants of interest in NGR1 (8p12, p=6.32E-08) and PAK6 (15q14, p=3.277E-07). Meta-analysis of NHW and AA results from lifetime pneumonia identified variants of interest in PRR27 (4q13.3, p=4.341E-07) and near MCPH (8p23.1, p=2.705E-07).

CONCLUSIONS
We have identified potential genes associated with risk of pneumonia. Further research will be required to determine whether these genes confer risk for childhood pneumonia, lifetime pneumonia and COPD.
INTRODUCTION

Pneumonia is a common pediatric diagnosis, especially in young children, that poses a significant risk for respiratory disease later in life.[1, 35] Pneumonia is less common in adults, though smokers are as sub-population known to experience increased rates of pneumonia.[36-40] Our prior investigations have demonstrated that pneumonia in childhood is a risk factor for chronic obstructive pulmonary disease (COPD), reduced lung function, and airway disease on chest computed tomography (CT) scans in adult smokers. This variability in prevalence of childhood pneumonia and the association with increased risk for COPD suggests an underlying genetic susceptibility.

There have been few prior investigations using genome wide association studies (GWAS) to investigate the genetic predisposition for pneumonia.[41] The objective of this study is to identify genetic susceptibility loci involved in the development of pneumonia in adult smokers from the COPDGene study population. We hypothesize that this case-control GWAS will identify susceptibility loci related to both childhood and lifetime pneumonia. Furthermore, we postulate that these loci are likely to have associations with genetic variants known to be related to COPD, asthma, lung function, lung development, and immune response.

METHODS

Subjects

We evaluated 10,192 current and former smokers in the US with and without COPD from the COPDGene Study, a multicenter, observational study designed to identify genetic and environmental factors associated with COPD. COPDGene enrolled subjects from 2008–2011. Subjects were between 45–80 years of age, of Non-Hispanic White or African American race,
and had at least a 10 pack-year history of smoking. Subjects were excluded if they had a history of lung disease other than COPD or asthma. COPDGene was approved by the Institutional Review Boards at each of the twenty-one clinical sites and all participants provided written informed consent.[16] The study protocol, enrollment criteria, and data collection forms have been previously described and are available at www.copdgene.org.[16, 17]

Data Collection

Phenotypic data was collected from subject responses to a modified American Thoracic Society Respiratory Epidemiology Questionnaire.[17, 18] Genotyping was performed on subject’s blood samples using the HumanOmniExpress platform (Ilumina, San Diego, CA). Additional genotypes were imputed from 1000 Genomes v3 reference panes using minimac and MaCH.[42-44]

Case Identification

Pneumonia was defined by subject self-report. The study questionnaire asked: “Have you ever had pneumonia or bronchopneumonia?” Subjects were classified as having had lifetime pneumonia if they responded affirmatively. Subjects were additionally asked the age at which they first had pneumonia, subjects were classified as having childhood pneumonia if they reported an age of first pneumonia at < 16 years or “As a child; age not known.” Subjects were classified as no history of childhood pneumonia if they reported no previous pneumonias, an age of first pneumonia ≥ 16 years, or if they did not indicated that their first pneumonia was during childhood. The age of 16 was used to define pediatric pneumonia in this study as this was when most subjects in the cohort started smoking (mean 16.9, standard deviation 4.6 years), which is
concurrent with a rise in the number of subjects reporting their first episode of pneumonia between 15-20 years of age.

**Statistical Analysis**

Independent GWAS were performed in subjects with childhood pneumonia and pneumonia at any point in their lifetime pneumonia using PLINK 1.90.[45] A logistic regression of single nucleotide polymorphisms (SNPs) based on case-control status was performed, adjusted for sex and genetic ancestry based on principal components (PCs).[46] Imputed genotypes were analyzed using SNP dosage data based on linkage disequilibrium. For each analysis lambda (λ) calculations were performed to assess the degree of population stratification after PC adjustment.[47] The imputational quality of SNPs was measured using r².[48] Initial evaluations were completed in the non-Hispanic white and African-American populations separately, and the results were subsequently combined in meta-analysis using a fixed effect model weighted by inverse variance.[45, 49] Power to detect an association in the meta-analysis was calculated using Quanto (Quanto version 1.2.4, May 2009).[50]

Top SNPs were assessed using R version 3.1.1.[51] In the individual population-based GWAS, SNPs with minor allele frequency (MAF) ≥ 5% were included for further analysis. For the meta-analysis, SNPs with MAF ≥ 1% were included.[49] Relationship of variants to associated genes was explored using the NCBI databases including dbSNP and Gene as well as LocusZoom.[52-54] The location of SNPs that had been found to be associated with COPD in prior GWAS were assessed in this population.[55]
RESULTS

Subject Classification

The COPDGene Study consists of 10,192 current and former smokers (Figures 1 and 2). Thirty-six subjects were excluded from this analysis, as it was not possible to classify their pneumonia history based on questionnaire responses. The 10,156 included subjects were divided into NHW (N = 6,766) and AA (N = 3,390) populations. Phenotype and genotype data from each population was merged. Subjects with phenotype data whose genotype data failed quality assessment were removed (114 NHW and 108 AA subjects excluded). Following the merge of the phenotype and genotype data, the remaining subjects were analyzed in individual GWAS.

For the childhood pneumonia analysis 6,652 NHW (685 cases; 5,967 controls) and 3,282 AA (158 cases; 3,124 controls), were included (Figure 1). Meta-analysis for childhood pneumonia was performed on the combined population, N = 9,934 (843 cases; 9,091 controls). The childhood pneumonia case-control meta-analysis was estimated to have 81% power to detect a SNP with an OR of 1.46.[50] For the lifetime pneumonia analysis, 509 additional subjects were excluded as they reported on survey response that they did not know whether they had a history of pneumonia. Subjects included in the lifetime pneumonia analysis were N = 6,306 NHW (2,284 case; 3,422 controls) and N = 3,119 AA (882 cases, 2,237 controls) (Figure 2). Meta-analysis for lifetime pneumonia was performed on the combined population, N = 9,425 (3,766 cases; 5,659 controls). The lifetime pneumonia case-control meta-analysis was estimated to have 82% power to detect a SNP with an OR of 1.26.[50]
GWAS of Childhood Pneumonia

The individual population based childhood pneumonia GWAS identified 5,870,826 SNPs with MAF ≥ 5% in NHWs (λ = 0.97) and 8,151,810 SNPs in AAs (λ = 0.89). QQplots and Manhattan plots can be viewed in the supplement (e-Figures 1 and 2). There were no SNPs that reached the level of genome-wide significance. The NHW analysis identified a couple of potential regions of interest. There was a region of interest on chromosome 1 that had fourteen SNPs with $p \leq 1 \times 10^{-7}$, clustered with an additional seven SNPs between $p \leq 1 \times 10^{-6}$ and $p \leq 1 \times 10^{-7}$. The genotyped variant with the lowest p-value was examined (rs11589302, $p = 4.304E-07$) (e-Figure 3). There was an additional potential region of interest on chromosome 15 (rs77554123, $p = 9.44E-06$, imputed). Both the chromosome 1 and 15 regions also reached near genome-wide significance in the childhood pneumonia meta-analysis, as described below. The AA GWAS for childhood pneumonia had no variants identified with $p \leq 1 \times 10^{-7}$. There were no SNPs associate with known COPD genes at near genome-wide significance.

Meta-analysis of NHW and AA results was performed including 6,950,410 SNPs with MAF ≤ 1% (QQ and Manhattan plots in e- Figure 4). There were no SNPs that reached the level of genome-wide significance, though potential regions of interest were identified. There was a variant of interest at near genome-wide significance in NGR1, neuregulin 1, at 8p12 (rs188808012, $p = 6.32E-08$, MAF NHW 1.5%, imputed with $r^2 0.95$) (Figure 3). Meta-analysis also identified the same regions of interest on chromosomes 1 and 15 that were previously seen in the NHW childhood pneumonia GWAS. One nearby gene to the chromosome 1 region (rs34223420, $p = 2.88E-06$, MAF NHW 5.2%, imputed) is MATN1, matrilin 1, cartilage matrix...
protein, at 1p35 (Figure 4). The chromosome 15 region (rs77554123, p = 3.277E-07, imputed) is in PAK6, p21 protein (Cdc42/Rac)-activated kinase 6, at 15q14 (Figure 5).

GWAS of Lifetime Pneumonia

The individual population based lifetime pneumonia GWAS identified 5,870,929 SNPs with MAF ≥ 5% in NHW (λ = 1.01) and 8,151,616 in AA (λ = 1.00). QQplots and Manhattan plots can be viewed in the supplement (e-Figure 5 and 6). There were no SNPs that reached the level of genome-wide significance, though potential regions of interest at near-genome wide significance were identified. In the NHW analysis, there was a region of interest on chromosome 8 that had two imputed SNPs with p ≤ 1 x 10^{-7} (rs11136992, p = 8.80E-07; rs55762539, p = 8.28E-07). This chromosome 8 region was also seen in the lifetime pneumonia meta-analysis, as described below. The AA GWAS for lifetime pneumonia showed 5 imputed variants of interest with p ≤ 1 x 10^{-7}, one on chromosome 3 (rs1107268, p = 8.67E-07), one on chromosome 6 (rs34476983, p = 6.06E-07), and three in a region on chromosome 4 (rs73860448, p = 8.87E-07; rs73860450, p = 8.92E-07; rs140541031, p = 8.40E-07). The three variants on chromosome 4 are associated with RAPGEF2, Rap guanine nucleotide exchange factor (GEF) 2, located at 4q32.1. There were no SNPs associate with known COPD genes at near genome-wide significance.

Meta-analysis of NHW and AA results from lifetime pneumonia was performed including 6,950,930 SNPs with MAF ≤ 1% (QQ and Manhattan plots in e-Figure 7). There were variants of interest at near genome-wide significance in a region of interest on chromosome 8 that was previously identified in the lifetime pneumonia NHW analysis, located near MCPH1, microcephalin 1, at 8p23.1 (rs11136992, 2.705E-07) (Figure 6). This meta-analysis also
identified a variant of interest in a different region of chromosome 4 associated with PRR27, proline rich 27, at 4q13.3 (rs56373127, 4.341E-07, imputed) (Figure 7).

**DISCUSSION**

We have identified potential genes and chromosomal regions of interest associated with the development of pneumonia both during childhood and over the course of the lifetime. In subjects with childhood pneumonia, there was enrichment of variants related to NGR1 (8p12), PAK6 (15q14) and a region of chromosome 1 near MATN1 (1p35). In subjects with lifetime pneumonia, there was enrichment of variants related to MCPH1 (8p23.1), PRR27 (4q13.3) and RAPGEF2 (4q32.1).

Prior investigators have identified genetic susceptibility to pneumonia largely based on candidate gene studies. Previous pneumonia GWAS related in humans have focused primarily on specific pneumonia pathogens or pneumonia related to sepsis.[56, 57] There are no previously documented GWAS related to overall pneumonia susceptibility.[41]

This study has used GWAS to identify genes potentially related to pneumonia susceptibility during childhood. NGR1 has an important role in organ system growth and development. It has been associated with GWAS related to lung function in the Framingham Heart Study.[58] PAK6 is plays a role in cytoskeleton rearrangement and apoptosis. MATN1 is related to extracellular matrix formation important in organ development.

The lifetime pneumonia GWAS also identified potential genes of interest. MCPH1 encodes a DNA damage response protein. RAPGEF2 functions in signal transduction and has been related
to pulmonary arterial hypertension.[53, 59] The top SNP regions associated the childhood and lifetime pneumonia analyses were different.

**Limitations**

We acknowledge that this investigation is limited by reliance on subject recall for classification of childhood pneumonia. A separate recall-bias assessment was conducted showing that individuals with a history of childhood pneumonia without known COPD or emphysema still had a significant decrease in lung function relative to those in the cohort who had never had pneumonia. Though it would be ideal to have primary data documenting the diagnosis of pneumonia during childhood, including medical records, chest x-ray, and pathogen information, that level of detail requires a prospective study design that starts at birth and would limit the ability to include older participants. However, 96.1% of subjects in the childhood pneumonia group did report that they had doctor-diagnosed pneumonia.

Another concern is the overall ability to detect significant variants at the genome-wide level. Though the COPDGene cohort includes over 10,192 subjects, only 843 have childhood pneumonia and a significant proportion overall is in the NHW population. GWAS can require populations of 10-20 times this size to detect significant variants.[60, 61] Despite this power limitation, there were a number of SNPs identified at near genome-wide significance that may be involved in critical pathways related to organ growth and development, lung function, and damage response.
CONCLUSIONS

The relationship between childhood pneumonia and respiratory disease in adult smokers is likely related to impaired lung growth and development, susceptibility to pulmonary infection and a genetic predisposition. This GWAS in current and former adult smokers identified potential genes of interest in subjects with a history of childhood and lifetime pneumonia that could help explain this relationship. Further exploration of the genetic susceptibility loci will be required to learn more about the pathways of disease association and to propose networks that of disease susceptibility based on these findings. The findings will also be confirmed in a replication population to further characterize their greater relevance.
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FIGURES

Figure 1: Subject Classification Childhood Pneumonia

[Diagram showing the classification process with numbers and categories for NHWs and AA individuals, including the final numbers for each category: 9,934 for Meta-analysis, 843 for Childhood Pneumonia, 9,091 for No Childhood Pneumonia, 6,670 for NHW Genotyped, 6,766 for NHW Phenotyped, 3,390 for AA Phenotyped, and 3,300 for AA Genotyped.]
Figure 2: Subject Classification Lifetime Pneumonia
Figure 3: LocusZoom Plot

Childhood Pneumonia Meta-analysis: CHR8, MAF 0.01 or greater

Figure 4: LocusZoom Plot

Childhood Pneumonia Meta-analysis: CHR1, MAF 0.01 or greater
Figure 5: LocusZoom Plot
Childhood Pneumonia Meta-analysis: CHR1, MAF 0.01 or greater

Figure 6: LocusZoom Plot
Lifetime Pneumonia Meta-analysis: CHR8, MAF 0.01 or greater
Figure 7: LocusZoom Plot

Lifetime Pneumonia Meta-analysis: CHR4, MAF 0.01 or greater
SUPPLEMENT

e-Figure 1: GWAS of Childhood Pneumonia in Non-Hispanic Whites (NHW)

a) QQ-plot (MAF ≥ 5%)

b) Manhattan Plot

e-Figure 2: GWAS of Childhood Pneumonia in African Americans (AA)

a) QQ-plot (MAF ≥ 5%)

b) Manhattan Plot
e-Figure 3: LocusZoom Plot

![LocusZoom Plot](image)

Childhood Pneumonia NHW: CHR1, MAF 0.05 or greater

e-Figure 4: GWAS of Childhood Pneumonia Meta-analysis

a) QQ-plot (MAF ≥ 1%)

![QQ-plot](image)

Childhood Pneumonia GWAS: Meta-analysis MAF ≥ 1% and P ≤ 0.05

b) Manhattan Plot

![Manhattan Plot](image)
e-Figure 5: GWAS of Lifetime Pneumonia in Non-Hispanic Whites (NHW)

a) QQ-plot (MAF ≥ 5%)  

b) Manhattan Plot

![QQ-plot](image1)  

![Manhattan Plot](image2)

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e-Figure 6: Plots for GWAS of Lifetime Pneumonia in African American (AA)

a) QQ-plot  

b) Manhattan Plot

![QQ-plot](image3)  

![Manhattan Plot](image4)
e-Figure 7: GWAS of Lifetime Pneumonia Meta-analysis

a) QQ-plot  

b) Manhattan Plot

Lifetime Pneumonia GWAS Meta-analysis MAF ≥ 1% and P ≤ 0.05