Fifty Years of Progress in the Epidemiology of Chronic Obstructive Pulmonary Disease: A Review of National Heart, Lung, and Blood Institute-Sponsored Studies

David M. Mannino, MD

Abstract
Our understanding of the epidemiology of chronic obstructive pulmonary disease (COPD), including such metrics as incidence, prevalence, risk factors, outcome, and comorbidities has increased greatly over the past 50 years. Much of this increase is attributable to National Heart Blood and Lung Institute (NHLBI)-sponsored studies. This paper will review 13 of these key studies and their contribution to our understanding of COPD in the last half century.

Keywords: National Heart, Lung, and Blood Institute; NHLBI; Division of Lung Diseases; epidemiology

Introduction
This year, marks the 50th anniversary of the Division of Lung Diseases of the National Heart, Lung, and Blood Institute, which from 1948 to 1969 had been known as the National Heart Institute, and by 1976 had its mission expanded and name changed to the National Heart, Lung, and Blood Institute (NHLBI). During the fifty years that the Division of Lung Disease has been in existence, the studies that it and other components of NHLBI have supported have contributed immensely to our understanding of respiratory disease in the population. The supported work ranges from large multigenerational cohort studies, such as the Framingham Study, to large clinical trials such as the Lung Health Study, to pooled studies that combine data from multiple cohorts.

This paper reviews the contributions of the National Institute of Health, and specifically the NHLBI and its Division of Lung Diseases to the understanding of the epidemiology of lung disease over the past half century. A challenge in determining this impact is that epidemiology is methods-based as opposed to being disease- or organ system-based, and the discipline thus
transcends a number of diseases and health topics. Thus, determining what is epidemiologic research is difficult in that the term “epidemiology” may not always be used in the title, abstract, or keywords of published studies. A PubMed search using the terms “Epidemiology”, “NHLBI”, and “Respiratory” OR “Pulmonary” OR “Lung” resulted in 897 publications (search done July 6, 2019), which would be well beyond the scope of this review. Accordingly, this review will focus on the key studies during this 50-year anniversary period, with an additional focus on work that improved our understanding of chronic obstructive pulmonary disease (COPD).

This review will look at 3 different general classes of studies: general population-based studies that included information on respiratory health, respiratory population-based studies that focused on respiratory health issues, and the Lung Health Study, which was a randomized control trial on smoking cessation but was extremely informative for the natural history of COPD. Several of these studies started prior to the creation of the Division Lung Disease in 1969 but are included as they have received ongoing support and have continued to make valuable contributions to the scientific literature over the past 50 years. Not included in this review are other important sources of information on the epidemiology of COPD, such as vital statistics data, hospitalization and health care utilizations, and survey-based research. In the United States, these types of studies have generally originated from the Centers for Disease Control and Prevention and the National Center for Health Statistics and are thus beyond the scope of this review.

**General Population Studies**

The prototype for the general population study is the Framingham Heart Study, which started in 1948 in the town of Framingham, Massachusetts (Table 1, Figure 1). The 1948 cohort included 5,209 people between the ages of 30 and 62. People in the study returned every 2 years for follow-up, and in 1971 a second generation of 5,124 participants, adult children and their spouses of the original cohort, were recruited. The study was also expanded in 1994, 2002, and 2003 to include additional people. As of April 2019, over 3,800 scientific publications have been published in the peer-reviewed literature using data from the Framingham Heart Study.

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**Figure 1. Timeline of Key Studies and the National Heart, Lung and Blood Institute**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1948</td>
<td>National Heart Institute (NHI) Established</td>
</tr>
<tr>
<td>1957</td>
<td>Tecumseh Study</td>
</tr>
<tr>
<td>1969</td>
<td>NHLI renamed National Heart and Lung Institute (NHILI)</td>
</tr>
<tr>
<td>1971</td>
<td>Framingham Heart Study Offspring Cohort</td>
</tr>
<tr>
<td>1972</td>
<td>Tucson Epidemiological Study of Airway Obstructive Disease</td>
</tr>
<tr>
<td>1976</td>
<td>NHILI renamed National Heart and Lung and Blood Institute (NHILB)</td>
</tr>
<tr>
<td>1980</td>
<td>Tucson Children's Study</td>
</tr>
<tr>
<td>1985</td>
<td>CARDIA</td>
</tr>
<tr>
<td>1986</td>
<td>Lung Health Study</td>
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<tr>
<td>1987</td>
<td>ARIC</td>
</tr>
<tr>
<td>1989</td>
<td>CHS</td>
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<tr>
<td>2000</td>
<td>MESA</td>
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<tr>
<td>2008</td>
<td>COPDGene</td>
</tr>
<tr>
<td>2010</td>
<td>SPIROMICS</td>
</tr>
<tr>
<td>2017</td>
<td>Pooled Cohorts Study</td>
</tr>
</tbody>
</table>
### Table 1. Key National Heart, Lung, and Blood Institute-Sponsored Studies and Their Findings Related to COPD

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Key Findings Related to COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham Heart Study²</td>
<td>1948</td>
<td>5209</td>
<td>Smokers have lower lung function and more rapid lung function decline.</td>
</tr>
<tr>
<td>Tecumseh Study¹²</td>
<td>1957</td>
<td>8641</td>
<td>Smokers have more cough and phlegm than never smokers. Male smokers have lower FEV₁ than never smokers.</td>
</tr>
<tr>
<td>Framingham Heart Study-Offspring Cohort⁹</td>
<td>1971</td>
<td>5124</td>
<td>Long-term lung function decline is 20 ml/year in men and 18 ml/year in women and is increased in smokers. About half of COPD cases occur in people who never attained their maximal lung function in early adulthood.</td>
</tr>
<tr>
<td>Tucson Epidemiologic Study of Airway Obstructive Disease¹⁷,¹⁸</td>
<td>1972</td>
<td>3805</td>
<td>Determined incidence and prevalence of COPD in a population sample.</td>
</tr>
<tr>
<td>Tucson Children’s Study¹⁹,²⁰</td>
<td>1980</td>
<td>246</td>
<td>Children with persistently low lung function are predisposed to COPD as adults.</td>
</tr>
<tr>
<td>CARDIA¹³</td>
<td>1985</td>
<td>5114</td>
<td>Respiratory symptoms in young adults increases risk of incident COPD, restriction, and emphysema.</td>
</tr>
<tr>
<td>Lung Health Study²³</td>
<td>1986</td>
<td>5887</td>
<td>Smoking intervention resulted in lower mortality at 14.5 years.</td>
</tr>
<tr>
<td>ARIC¹⁴</td>
<td>1987</td>
<td>15,368</td>
<td>People with COPD are more likely to die from comorbid disease than from COPD. People with COPD and high fibrinogen levels have more exacerbations. Also included data from CHS.</td>
</tr>
<tr>
<td>Cardiovascular Health Study¹⁵</td>
<td>1989</td>
<td>5888</td>
<td>Comorbid hypertension, diabetes, and cardiovascular disease is higher in COPD and increases the risk of hospitalizations and death. Also included data from ARIC.</td>
</tr>
<tr>
<td>MESA¹⁶</td>
<td>2000</td>
<td>7071</td>
<td>Examined the relationship between emphysema and right ventricular structure, pulmonary hyperinflation and left ventricular mass, and lung function and QT duration. COPD patients with larger airway dimensions have a higher risk of exacerbations.</td>
</tr>
<tr>
<td>COPDGene²¹</td>
<td>2008</td>
<td>10,192</td>
<td>COPD patients with pulmonary artery enlargement or central airway collapse have a higher risk of exacerbations. Acute exacerbations lead to accelerated loss of lung function. Identified genetic loci associated with COPD, emphysema, chronic bronchitis, and emphysema. Identified restrictive physiology (PRISm) as a potential transitional state between health and COPD.</td>
</tr>
<tr>
<td>SPIROMICS²¹</td>
<td>2010</td>
<td>2981</td>
<td>Determined genetic risk score for COPD-related to computed tomography findings. Also included data from MESA. People with restrictive physiology have exacerbations, activity limitation and airway disease.</td>
</tr>
<tr>
<td>Pooled Cohort Study⁶</td>
<td>2017</td>
<td>65,251</td>
<td>The fixed ratio of FEV₁/FVC of 0.70 discriminates people at risk for COPD-related hospitalization and mortality. Albuminuria associated with higher risk of lung function decline, incident COPD, and COPD-related events.</td>
</tr>
</tbody>
</table>

COPD=chronic obstructive pulmonary disease; FEV₁=forced expiratory volume in 1 second; CARDIA=Coronary Artery Risk Development in Young Adults study; CHS=Cardiovascular Health Study; ARIC=Artherosclerosis Risk in Communities; MESA=Multi-Ethnic Study of Artherosclerosis; COPDGene⁴=Geneic Epidemiology of COPD; SPIROMICS=Subpopulations and Intermediate Outcomes in COPD Study; FVC=forced vital capacity.
The Tecumseh Study, based in the town of Tecumseh, Michigan, was similar in design to the Framingham Heart Study, commencing in 1957. It enrolled 8641 people, of whom 5140 were over the age of 16.11,12

Subsequent large population-based cohorts included the Coronary Artery Risk Development in Young Adults (CARDIA) study in 1985,13 the Atherosclerosis Risk in Communities (ARIC) study in 1987,14 the Cardiovascular Health Study (CHS) in 1989,15 and the Multi-Ethnic Study of Atherosclerosis (MESA) in 2000.16 While all of these studies had a cardiovascular disease focus, they also included spirometry testing at baseline and at some of the follow-up examinations.

Additional work has pooled data from the Framingham Heart Study Offspring cohort, the CARDIA, ARIC, CHS, MESA cohorts and 4 additional cohorts into the NHLBI Pooled Cohort Study comprising over 65,000 adults with over 650,000 person years of follow-up.4

**Key Findings**

Several key findings of the NHLBI-sponsored studies are noted below, grouped by general category. This listing is not intended to be comprehensive, but to highlight some of the important areas where these studies have increased our understanding and provided a pathway for targeted interventions and better therapies.

**Respiratory Health Effects Due to Smoking**

When the 1964 Surgeon General’s report on Smoking and Health was published, COPD was not widely used as a disease term and the relationship between cigarette smoking and respiratory disease was still being established.26 The report concluded that cigarette smoking causes chronic bronchitis, increases the risk of dying from chronic bronchitis, and is more important than air pollution as a cause of chronic bronchitis for most of the U.S. population.26 The report did not establish a causal relationship between cigarette smoking and emphysema.

Findings from the Tecumseh study were critical in establishing the initial relationship between cigarette smoking, respiratory symptoms, and lung function.12 They found that the respiratory symptoms of cough and phlegm increased with current smoking and age among both men and women.12 They also found that the forced expiratory volume in 1 second (FEV1) measurement was decreased among male smokers, relative to male never smokers, but did not see an effect in female smokers.12

Similarly, the Framingham Heart Study demonstrated lower lung function among both men and women when smokers were compared to nonsmokers.27 This study also demonstrated more rapid lung function decline.27

A second category of key studies that have increased our understanding of COPD are the population-based studies that were focused on respiratory disease in their development and implementation. The prototype for this type of study is the Tucson epidemiologic study of obstructive lung diseases, which enrolled 3805 in 1972.17,18

An extension of this study, the Tucson Children’s Respiratory Study, enrolled 1246 newborns starting in 1980 and has now followed this cohort into young adulthood.19,20

The largest COPD specific cohort study, the Genetic Epidemiology of COPD (COPDGene) study, commenced in 2008 and has enrolled 10,192 patients, most of whom have COPD.21 This study was designed to better understand the genetic factors that lead to the development of COPD, but its inclusion of imaging and other markers of COPD has resulted in a number of insights into COPD development and progression.

The final study in this category, Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS), is an observational study of COPD designed to provide better phenotypic classification of disease in a cohort.22 This study commenced in 2010 and has enrolled 2981 patients.

**The Lung Health Study**

The Lung Health Study, which was designed as a randomized clinical trial to examine the effect of smoking cessation and bronchodilators on COPD outcomes provided a great deal of information on the natural history of COPD.23 In 1986, the study recruited 5887 smokers aged 35 to 60 years with spirometric evidence of mild COPD and followed them in a 3-armed trial for 5 years. Patients were reevaluated 11 years after recruitment with spirometry24 and mortality was assessed at 14.5 years.25
Long-term follow-up of the Lung Health Study demonstrated that a smoking cessation intervention resulted in a significant reduction in mortality at 14.5 years, even though this intervention was only successful in a minority of patients.  

**The Natural History of COPD and Lung Function**

When Fletcher and Peto described the natural history of lung function decline in 1977, their observations were based on a cohort of British men who were followed for 8 years. Long-term follow-up of the Framingham Offspring study was able to extend these observations to women and calculate a better estimate of long-term lung function decline of 20 ml/year in healthy never-smoking men and 18 ml/year in healthy never-smoking women. The Framingham Offspring Study was also part of an analysis demonstrating that about half of COPD cases occur in people who never reached their best potential lung function in early adulthood, suggesting the early life factors are important in the development of COPD. The Tucson Children’s Study independently demonstrated that some children have consistently low lung function that persists into adulthood, increasing their risk of developing COPD.

The Tucson Epidemiologic Study of Airway Obstructive Disease was critical in establishing the incidence and prevalence of COPD, using both clinical and spirometric criteria, in a general population sample. More recently, the Pooled Cohort Study has taken a critical look at how COPD is defined, and determined that the fixed ratio of 0.70 for the FEV₁/FVC ratio provided discrimination of COPD-related hospitalization and mortality that was not significantly different or was more accurate than other fixed thresholds and the lower limit of normal.

**Comorbidity and Polymorbidity in COPD**

The role of comorbid disease in COPD has been critical to the understanding of disease progression and outcomes in COPD. For example, analysis of ARIC data showed a relationship between severity of lung function impairment and long-term mortality, and also demonstrated that at all levels of impairment people were more likely to die of diseases other than respiratory ones. This was true even for those with severe COPD at baseline.

Another important contribution from ARIC and CHS is the relationship between COPD and several common comorbid diseases. One analysis demonstrated that comorbid hypertension, diabetes, and cardiovascular disease is more prevalent in COPD and increases the risk of hospitalizations and death.

MESA has had several important contributions related to cardiovascular comorbidity. These include the relation between emphysema and right ventricular structure, pulmonary hyperinflation and increased left ventricular mass, and lung function and increased QT duration on the electrocardiogram.

Finally, the Pooled Cohort Study examined the relationship between albuminuria and lung function and found that higher levels of albumin in the urine were associated with more rapid lung function decline, incident COPD (defined spirometrically), and incident COPD-related events.

**COPD Exacerbations – Risk Factors and Outcomes**

Exacerbations of COPD are important events that can lead to a number of adverse outcomes in patients and are part of the classification scheme that the Global initiative on chronic Obstructive Lung Disease (GOLD) uses to classify disease severity and guide therapy.

Risk factors for exacerbations include high fibrinogen levels, as demonstrated in the ARIC and CHS cohorts, pulmonary artery enlargement and central airway collapse, as demonstrated in COPDGene, and larger airway dimensions, as demonstrated in MESA.

Information on outcomes related to COPD exacerbation events are also important contributions of these databases. For example, analysis of data from ARIC and CHS demonstrated that hospitalized COPD exacerbations increase the risk of mortality regardless of COPD stage at baseline, and COPDGene data demonstrated that exacerbations lead to accelerated lung function decline, particularly among people with mild disease.

**The Genetics of COPD**

COPD, like most chronic diseases, is influenced by both genetic and environmental factors, although our understanding of COPD has been much more focused, historically, on the environmental factors. This gap is being addressed, in part, by the COPDGene study. This study, which now has a decade of follow-up, has identified over 20 genetic loci associated with COPD.
affectation status, along with additional loci associated with COPD phenotypic characteristics, including emphysema, chronic bronchitis, and hypoxemia.  

Other studies have also contributed to our understanding of the genetics of COPD. For example, data from MESA and SPIROMICS is used to examine the association between a genetic risk score developed for COPD and lung structure on computed tomography scans.

**Early or Atypical COPD**

Other critical gaps that are being addressed are those looking at early or atypical disease. The role of childhood exposures in the development of COPD, demonstrated in the long-term follow-up of the Tucson Children’s study, was noted above.  Looking at a young adult population, the CARDIA study has demonstrated that young adults with respiratory symptoms are more likely to have accelerated lung function decline, the development of obstructive or restrictive physiology, and a higher risk of development of radiographic emphysema.

A growing body of evidence suggests that patients who don't meet the classic spirometric definition of COPD may still share features of COPD and may respond to therapy. This group of patients, with findings of restrictive physiology (also known as preserved ratio impaired spirometry [PRISm] or GOLD U) have been investigated in these cohorts. SPIROMICS found that they have exacerbations, activity limitation, and evidence of airway disease. In the COPDGene® study these patients had a higher risk of mortality and may represent a transitional state between health and COPD.

**Summary**

NHLBI-sponsored studies have made many important contributions to our understanding of the epidemiology of COPD over the past 50 years. Many of these cohorts remain active and can be expected to add to our understanding of how COPD develops and progresses. The next 50 years will, hopefully, move us towards better identification of early disease, finding biomarkers that inform us of disease risk and progression, and, ultimately, finding a cure for this disease.

**Declaration of Interest**

Dr. Mannino is a full-time employee and shareholder of GlaxoSmithKline. The opinions expressed in this paper are those of the author and do not necessarily represent those of GlaxoSmithKline.
References


