Chronic Obstructive Pulmonary Disease: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases

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Abstract

Chronic obstructive pulmonary disease (COPD) is a complex set of conditions with multiple risk factors, disease mechanisms, and clinical manifestations. These characteristics make primary prevention of COPD challenging. Semantic issues related to prevalent and incident disease (e.g., the use of specific cut points on a continuous range) should not derail development of primary prevention initiatives. Potential targets for COPD prevention occur along the spectrum of disease development. Understanding risk factors early in life, whether specific to COPD or not, allows for study of interventions to optimize lung function at birth and to prolong the lung function plateau, potentially reducing the development of COPD. It is necessary to identify noninvasive ways to screen for early

COPD in those at risk before progression to clinically significant disease. Identification of specific COPD subgroups, such as individuals with chronic bronchitis, those with α_1 -antitrypsin deficiency, or early radiographic changes with normal spirometry, may offer specific opportunities for primary prevention. A better understanding of why COPD progresses despite smoking cessation is needed. Future research initiatives should also focus on identifying the underlying mechanisms and relevant interventions for nonsmokers with COPD, a currently poorly studied group. Ultimately, preventing the development of COPD will serve to reduce the tremendous burden of this chronic disease worldwide.

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Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by airflow limitation associated with debility and death. COPD is now the third leading cause of death in the United States, and is projected to be the third leading cause of death worldwide by 2020 (1). The majority of research and therapeutic interventions focus on treating COPD after it has developed. There has been limited focus on the *primary prevention* of COPD. Present evidence suggests that avoidance of tobacco smoke and other inhaled particulates and toxins is the most important way to prevent the development of COPD. Prevention of smoking initiation and promotion of

smoking cessation should be included in any program of COPD primary prevention. The following discussion reviews the current state of COPD primary prevention, and identifies gaps and priorities beyond smoking cessation in the prevention of COPD.

The Challenges of Understanding What Is Meant by “COPD”

There are several potential definitions of COPD used in clinical and research settings (2–5). The clinical assessment that is commonly used when evaluating a patient

in the healthcare setting, which is based on symptoms of cough, sputum, dyspnea, and fatigue, is not recommended to establish a diagnosis of COPD, as these features do not reliably predict airflow limitation. Formal spirometric criteria are recommended to determine the presence or absence of COPD in clinical and research settings. However, there is debate regarding the most appropriate definition (6–8). The most widely used spirometric criteria define obstruction using a fixed-threshold criterion of postbronchodilator spirometry (2) (i.e., GOLD [Global Initiative for Obstructive Lung Disease] based on post-bronchodilator forced expiratory volume in 1 s [FEV₁]/forced vital capacity [FVC]

<70%, with specified cut points for levels of severity using percent predicted values). This approach, favored for its ease of applicability, is disadvantaged by the arbitrary nature of the threshold and lack of strong scientific rationale (9). Other organizations, including the American Thoracic Society, COPD Foundation, the American College of Chest Physicians, the American College of Physicians, and the European Respiratory Society use different criteria to define the presence of disease (less than the lower limit of normal), as well as levels of severity (5). The global Burden of Obstructive Lung Disease study promotes that criteria based on percent predicted introduce serious misclassification, and instead uses lower limit of normal for all of the metrics, as this is a more statistically robust way of categorizing airflow obstruction (3).

In addition to spirometric definitions, radiographic criteria have recently been used to identify COPD. Inspiratory and expiratory computerized tomography (CT) scans can be used to define specific patterns of both emphysema-predominant and airway-predominant disease, which have been shown to correlate with relevant clinical findings, such as dyspnea, decreased quality of life, and exercise capacity (10–12). Each of the definitions currently applied to research and clinical practice have unique strengths and limitations. When considering primary prevention of COPD, it is necessary to first determine the most appropriate definition of COPD.

COPD Can Be Considered a Categorical or Continuous Disease Process

Complicating the challenge of defining incident COPD is the reality that COPD is defined with a dichotomous threshold, but actually occurs on a continuum. In the context of COPD, the concept of incident disease depends upon the metrics used to define it. The term “preclinical disease” is difficult to define, given the lack of standard diagnostic approach. It remains to be determined whether variations in “normal” represent early transition to disease. Similarly, to date, the presence of disease in an individual has been defined in terms of an absolute value relative to a population, rather than change from a personal baseline. It remains unclear whether

symptomatic disease without spirometric abnormalities represents incident disease, or whether spirometric changes that do not reach the disease threshold should be considered abnormal or whether the combination of the two has particular significance. The development of chest CT to assess lung structure extends these problems to a new dimension. CT can identify significant emphysema and/or gas trapping in 20–30% of heavy smokers whose FEV₁ and FEV₁/FVC are within the normal range. It remains unclear where on the continuum from health to disease individuals with these observations should fall. There are little data on the impact of alternative definitions of disease as they relate to the continuum of COPD, and how they relate to primary prevention.

A related issue is the distinction between “early” disease and “mild” disease, which are often confounded in common parlance. This distinction becomes clear when looking at longitudinal data, for example the Lung Health Study (13). A significant proportion of those entering the study with mild airflow obstruction did not show an accelerated decline in lung function over the 11-year follow-up. These individuals presumably had “mild” disease rather than “early” disease. Many studies of COPD include primarily individuals in the sixth and seventh decades of life. Those with minimal decrements in lung function have “mild” disease, but it is very unclear that it is “early” disease. Identification of individuals with “early” disease may require evaluation at a much younger age than that at which COPD is currently studied.

COPD Is a Heterogeneous Disease

Primary prevention of COPD necessitates an understanding of the risk factors, pathological findings, and clinical manifestation of disease. All these are distinctly heterogeneous (14). Multiple different exposures can lead to the same final condition, but quantifying exposures is often difficult. For example, among cigarette smokers, there is marked heterogeneity in duration, intensity, and composition of toxins from one smoker to another. The individual response to that exposure also varies markedly from individual to individual, due either to genetic differences or to other

environmental influences (e.g., diet). Recognition of mechanistic heterogeneity is essential for preventive efforts designed to interrupt causative pathways, as interventions that may prevent COPD in one subgroup may be ineffective (or worse) in other groups at risk of developing COPD.

Regardless of the definition used to define the disease state in the clinical and research setting, COPD is characterized by limitation of expiratory airflow. At the pathological level, at least three histological lesions, which are present to varying degrees of severity in different individuals, can contribute to airflow limitation and pulmonary symptoms: (1) hypertrophy of airway glands and goblet metaplasia of the airways (a characteristic feature of chronic bronchitis); (2) fibrosis, narrowing, and loss of small airways; and (3) destruction of alveolar wall, the defining feature of emphysema (15). Additional histologic lesions may be present. For example, extensive injury and destruction of the pulmonary vascular bed occurs, with pulmonary hypertension being a serious complication in some individual with COPD.

Although several lesions can lead to airflow limitation, the associated clinical features, including the symptoms of cough, sputum, and dyspnea, susceptibility to exacerbations, and systemic manifestations, differ markedly among individuals (16). In parallel with the anatomic and clinical heterogeneity, patients with COPD manifest heterogeneity for presumed markers of pathobiology, including measures of inflammation in the lung and systemically. Moreover, it is likely that several distinct inflammatory and immune processes, including autoimmunity, play roles in subsets of patients with COPD. Although a full description of COPD heterogeneity is still lacking, several recent analyses suggest that there are multiple distinct subsets of patients with COPD that likely differ anatomically, clinically, and mechanistically. The heterogeneity of COPD extends beyond the pulmonary system, and includes the spectrum of comorbidities associated with COPD. Prevention of COPD may prevent the development of other diseases, and similarly, treatment of comorbidities may prevent COPD development. Heterogeneous mechanisms may be targets for future interventions, and specific

biomarkers may exist to predict future disease development in certain subsets of patients with COPD. For primary prevention of COPD, one must consider both population-based approaches (e.g., improving overall lung health or decreased smoking initiation) as well as personalized approaches (eg, α_1 -antitrypsin replacement).

Proposed Mechanisms of COPD Development

Current concepts suggest that COPD results from lung injury that exceeds the ability of lung repair mechanisms to restore tissue structure and function (17–20). Inflammation is thought to be the major cause of lung damage in COPD (21, 22). Disruptions in tissue maintenance and repair have also been demonstrated in COPD. There are many unanswered questions about mechanisms of disease pathogenesis in COPD. Evidence supports roles for oxidative stress, protease-mediated damage, activation of inflammatory cells, and apoptosis, but the relevant molecular and cellular pathways remain largely undefined. Genetic factors contribute to COPD, but the role for specific genes remains largely unknown. Cigarette smoke and other exposures are well established inducers of inflammation of the type most commonly observed in COPD, which includes expansion and activation of alveolar macrophages, neutrophils, and CD8⁺ lymphocytes (23–26). It is likely, however, that other inflammatory cells also play key roles, particularly in subsets of patients with COPD (27). For example, relatively high levels of eosinophils may identify a population of patients responsive to inhaled glucocorticoids. Both innate and acquired immunity likely play roles, and in some individuals, autoimmune processes have been observed. Cigarette smoke, and likely other exposures, can also disrupt tissue maintenance and repair. Finally, normal function of lung structural cells requires interaction with extracellular matrix. How these factors interact with sex and nutrition is also unknown. It is certain, however, that these factors will be of variable importance in different individuals. Thus, individuals will vary in their susceptibility and in the mechanisms involved based on both genetic and environmental modifiers.

Identifiable Risk Factors for COPD

Establishment of a risk factor or biomarker that can be used for early identification of susceptibility and progression of disease from dysregulation to symptomatic disease requires several key steps. Risk factors and biomarkers must be identified in individuals with disease or those who ultimately develop disease, link to plausible mechanistic pathways, and be modifiable in a manner correlative with disease presence. Several risk factors for COPD can be modified, thus preventing the development of chronic lung disease. These modifiable risk factors can be conceptualized within the framework of the life course model of disease development. Data exist indicating that events as early as the prenatal and antenatal period of life can modify COPD risk. Socioeconomic status and maternal nutritional status is associated with future lung health (28, 29). Decreasing direct insults to the lung during early life, including prevention of smoking initiation and environmental exposures, also may serve to prevent COPD development. Infections, both respiratory-specific infections and infection with human immunodeficiency virus, have been shown to be associated with increased prevalence of COPD, as well as more rapid lung function decline (30, 31). Controlling the chronic inflammatory response to inhaled pollutants or infectious insults may serve as preventable risk factor for COPD development. Finally controlling exposures to smoke and other environmental insults should reduce risk of development of COPD.

Although genetic risk factors are typically viewed as nonmodifiable, some genetic traits can be viewed as causing disease that can be modified. α_1 -Antitrypsin is a model of an established genetic risk factor for COPD, the course of which can be modified with protein replacement (32). Genetic biomarkers may identify individuals susceptible to COPD and provide opportunities to prevent disease before disease onset. Interestingly, some genes linked to COPD development appear to be genes related to nicotine addiction, and thus may be linked to COPD development through a propensity to smoke. It may be possible to treat such individuals to prevent smoking initiation.

Major Gaps and Areas of Immediate and Long-Term Research for COPD Primary Prevention

Given the unique challenges in defining the risk factors, onset, manifestations, and mechanisms underlying COPD, several priority areas for research into the various stages of COPD natural history are present. In particular, although the natural history of COPD often focuses on the progressive phase of the disease, the growth and development of the lung is a major determinant of COPD risk and an appropriate target for primary prevention (Figures 1 and 2). The maximal level of lung function attained in early adulthood may be a critical component of an individual reaching a level of lung function at which there is clearly functional impairment.

The following section identifies major gaps in COPD primary prevention and potential research questions to address these gaps.

1. Understanding How Growth and Development of the Lung Impacts the Risk of COPD Development

We need to know the early prenatal, early childhood, and adolescent exposures (e.g., nutritional, allergic, infectious, toxic) and other factors (e.g., prematurity, genetic, sex, socioeconomic, asthma) that affect duration of lung function plateau and maximally attained adult function. We then need to evaluate which might be targets for healthcare or health policy interventions, and conduct studies to determine whether they can be modified, and, finally, if such modification prevents the development of COPD. This will be facilitated by confirming if maximally attained lung function is a risk factor for development of COPD. Similarly, it will be important to determine if interventions that improve maximally attained lung function reduce risk of COPD development.

Potential research topics.

- Leverage existing general population studies and childhood cohorts that have already been studied longitudinally to determine early life factors impacting lung function.
- Explore existing cohort data of adults to determine if maximally attained lung

Figure 1. Lung development and growth and chronic obstructive pulmonary disease (COPD) risk. Intrauterine events can compromise lung growth (*dashed line*). Events in childhood and adolescence can compromise lung growth (*dotted line*). Both of these can alter maximally attained lung function. The relationships between intrauterine development and growth and lung growth in childhood and adolescence are unknown, but could interact to further compromise maximally attained lung function. In most individuals, lung function generally remains at the maximally attained function achieved in young adulthood for 10 years or so, then gradually declines. Whether this is “normal” or represents the consequence of pathological processes is unknown. Shortened duration of the plateau of lung function will result in lower lung function with aging (*solid lines*). These *lines* are drawn starting from the same level to emphasize the effect of the shortened plateau. If a shortened plateau were related to alterations in maximally attained lung function, the risk for reduced lung function would be greater. FEV₁ = forced expiratory volume in 1 second.

function impacts risk of COPD development.

- Extend existing childhood cohorts into adulthood to determine predictors or risk factors for COPD development.
- After establishment of risk factors, perform efficacy studies to determine whether these risk factors can be modified, if such modification improves lung function, and establish whether screening for risk factors and making interventions are effective and cost efficient in a real-world setting.

2. Identifying Mechanisms to Screen for Early COPD that Will Progress to Clinically Significant Disease

There is a need to identify clinical presentations, noninvasive biomarkers, physiologic measures, or radiographic abnormalities present antecedent to development of clinically significant disease. Several studies suggest that this is readily feasible. CT scanning can identify radiographic abnormalities characteristic of emphysema and/or airways disease that are present in individuals with airflow in the

“normal” range. Whether these individuals will progress to develop airflow limitation and, therefore, COPD is essential to understand. In this context, although controversial, individuals with persistent chronic bronchitis have been described as being at increased risk to develop airflow limitation.

Potential research topics.

- Interventional studies to determine if treatments that target persistent bronchitis prevent the development of COPD. Such studies should be integrated with investigation of the role of biomarkers to predict lung function decline and response to therapy and to studies to determine basic mechanisms of disease.
- Testing of putative biomarkers of early disease identified in basic/translational projects within existing clinical or research cohorts with phenotypic characterization of at-risk smokers.
- Long-term studies that define the prognostic importance of measurable changes in lung function and structure that are generally regarded as being in

the normal range, both within an individual and in comparison to the general population.

- Develop better methods of identifying lung dysfunction in early life, including *in utero* and childhood, such imaging techniques that are practical and ethical in these age groups that can identify airway and parenchymal abnormalities.

3. Identify Risk Factors for COPD Development despite Smoking Cessation

We need to have a better understanding of why COPD often develops and progresses after cessation of smoking. Why does the chronic inflammation continue when the putative stimulus is removed, and how can this be changed. A related question is whether the inflammation is the proximate driver of COPD progression or the result of established disease. If the former, the mechanisms that account for COPD progression other than chronic inflammation needs to be defined.

Potential research topics.

- Mechanistic and epidemiological characterization of the lung (inflammation, function) after smoking cessation and how these factors impact development of incident COPD.
- Testing of pharmacological interventions (e.g., long-acting β agonist/inhaled corticosteroids, N-acetylcysteine, long-acting muscarinic antagonists, azithromycin) in individuals with normal FEV₁ and FEV₁/FVC ratio who have early symptoms (e.g., cough and phlegm) to determine if these interventions decrease risk of progression to spirometry-defined COPD.

4. Characterizing the Varying Phenotypes of Nonsmoking COPD and Smoking-related COPD

COPD is clinically, anatomically, and mechanistically heterogeneous. It is likely that there are many subtypes of COPD, and that these will require different prevention strategies. We need better understanding of the risk factors that lead to specific subtypes of COPD in nonsmokers and smokers. Nonsmokers with COPD are very poorly understood. Nevertheless, several risk factors have been identified that create opportunities for prevention. For example,

Figure 2. The progression of chronic obstructive pulmonary disease (COPD) is incompletely understood. COPD, characterized by reduced lung function, may develop through several natural histories. Theoretically, some individuals may lose lung function at an accelerated rate throughout life (*curve A*), some may progress like “normal” for some time, then enter a period of very accelerated loss of function (*curve B*), and some may have acute exacerbations that eventually compromise lung function (*curve C*) (33). These natural histories are not easily distinguishable when the disease is clinically apparent in the 50s or 60s. It is now recognized that some individuals with COPD may improve, at least modestly, but consistently, over several years (*dashed line, curve D*) (34). Graphic modified from Burrows (33), which was modified from Fletcher and Peto (35). FEV₁ = forced expiratory volume in 1 second.

asthma can progress to COPD. Whether interventions designed to control tissue remodeling in asthma can prevent the development of COPD is a question that needs to be addressed. Nonsmokers with COPD, however, include patients with no known exposures and no asthma history. Understanding the risk factors, developing methods to identify these individual early in the course of their illness, and defining the mechanisms involved is needed.

Potential research topics.

- Use existing cohorts (e.g., Burden of Obstructive Lung Disease study, Proyecto LatinoAmericano de Investigación en Obstrucción Pulmonar, Multi-Ethnic Study of Atherosclerosis, Honolulu Heart Study, Framingham Heart Study) to perform cross-sectional studies to understand prevalence, risk factors, and characteristics of nonsmoking COPD.
- Longitudinal study of normal people (nonsmokers or smokers) at age 40–50 years with COPD-specific outcomes

(imaging, biomarkers, genomics) to define features before developing COPD.

- Harmonize with ongoing or newly proposed cohort studies in other specialties (e.g., cardiology, nutrition) to include lung-specific outcomes as key endpoints.

5. Understanding How Nutritional Status Impacts the Risk of COPD Development

Observational data suggest that compromised nutritional status increases risk of lung disease, and that nutritionally based treatment may improve overall lung health. It remains unclear if there are specific macro- or micronutrients that may specifically prevent the development of COPD in at-risk individuals. Identifying efficacious nutritional interventions would allow for additional therapeutic options in at-risk individuals.

Potential research topics.

- Determination of the role of macro- and micronutrients on the development of COPD. It is likely that nutritional effects will need to be assessed

specifically at various stages of COPD natural history.

- Proof-of-principle intervention studies of macro- or micronutrient supplementation with intermediate biomarker endpoints, case-control studies of existing cohort studies with nutrient intake data, and definitive randomized clinical trials with nutrients for which there is sufficient preliminary data.
- Leverage existing long-term cohort studies of patients at risk for COPD (e.g., cohorts with asthma or nutritional deficiencies) to determine specific risk factors for COPD that may be modified.

Overall Priorities for Research

COPD is a disease that manifests itself most commonly in the sixth and seventh decades of life. There is little doubt, however, that the disease process begins in very early life and is modified by events throughout childhood, adolescence, and adulthood.

Methods are now available that can determine variations within populations before clinically apparent COPD is manifest. It is essential that the importance of these measures, both in comparison to the general population and as changes within an individual, be understood. However, the indolent development and progression of COPD creates inherent challenges in efficient epidemiological and clinical trial design within conventional funding timelines. Several alternative approaches, however, offer opportunities to pursue these goals: (1) leveraging existing data and infrastructures for efficient study design, including partnerships with nongovernment and government organizations; (2) relating potential early measure of lung disease to all phases of life that lead to risk of COPD, including prenatal, antenatal, and early life events; (3) validation of biomarkers that could serve as shorter-term measures of COPD risk and progression; and (4) exploitation of opportunities that exist for interventions designed to prevent COPD development should be given high priority, and should be funded for a sufficient duration that is likely to be longer than that in most current grant proposal. Intervention studies are particularly valuable, as they can include components

that will advance understanding of biomarkers that predict outcome and of disease mechanisms. Finally, it is important to recognize that novel clinical cohorts may be required in addition to leveraging existing ones to accomplish these goals.

Understanding of the development of COPD and its progression can be achieved if all phases of COPD natural history are studied in parallel studies concurrently. The alternative (felt to be unacceptable) is a study that requires 70 years' duration. It is essential that the "parallel" studies be well integrated. This will require not only a commitment to data sharing, but also the use of easily harmonized methods and database structures. This integration should be included conceptually and practically in all studies from the beginning. The near-term (next 5 yr) and long-term (next 5–10 yr) priorities for research in primary prevention of COPD are summarized in Table 1. Near-term priorities were selected as they represent the most immediately feasible deliverables that provide the foundation for future studies of COPD primary prevention. Long-term priorities were selected as they represent the progression of knowledge gained from the data collected from pre-existing data.

COPD is a major public health problem in the United States and

Table 1. Recommendations for research priorities for the primary prevention of chronic obstructive pulmonary disease

Near-term priorities (next 5 yr)

- An identification of existing NHLBI cohort studies with lung data, allowing for researchers to identify suitable cohorts to address scientific gaps identified earlier.
- Development of an online registry of cohort studies (analogous to www.clinicaltrials.gov).
- Active engagement with other Divisions and Institutes to include pulmonary outcomes in cohort studies, the primary focus of which may be outside of COPD.
- Evaluation of maternal/fetal health interventions as they pertain to general lung health and COPD. This will require a cohort study that follows individuals from pregnancy until puberty.
- Identification of early biomarkers and imaging to detect preclinical disease. This should include evaluation of individuals aged 40–50 years without lung disease who are followed long enough for COPD to become manifest.
- Intervention studies to determine if progression of persistent chronic bronchitis to COPD can be prevented.
- Interventions to prevent development of emphysema in individuals genetically at risk to develop emphysema (e.g. α_1 -antitrypsin).

Long-term priorities (next 5–10 yr)

- Extension of observational studies of adolescent and young adults into age ranges where incident COPD develops.
- Intervention studies of novel and established pharmacotherapies that may impact risk factors defined from new observational studies.
- Intervention studies in preclinical COPD to reduce development of incident COPD.

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; NHLBI = National Heart, Lung, and Blood Institute.

worldwide. Its public health impact is likely to increase over the coming years. Cigarette smoking is the major cause, but only accounts for about one-half of the attributable risk, so advances in primary prevention are essential. Because COPD develops over the entire human lifespan, studies of its natural history and prevention

are daunting. Nevertheless, recent advances in understanding present realistic opportunities to advance prevention efforts to reduce the burden imposed by this devastating condition. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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