Promotion of Lung Health: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases

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Abstract

Lung-related research primarily focuses on the etiology and management of diseases. In recent years, interest in primary prevention has grown. However, primary prevention also includes “health promotion” (actions in a population that keep an individual healthy). We encourage more research on population-based (public health) strategies that could not only maximize lung health but also mitigate “normal” age-related declines—not only for spirometry but across multiple measures of lung health. In developing a successful

strategy, a “life course” approach is important. Unfortunately, we are unable to achieve the full benefit of this approach until we have better measures of lung health and an improved understanding of the normal trajectory, both over an individual’s life span and possibly across generations. We discuss key questions in lung health promotion, with an emphasis on the upper (healthier) end of the distribution of lung functioning and resiliency and briefly summarize the few interventions that have been studied to date. We conclude with suggestions regarding the most promising future research for this important, but largely neglected, area of lung research.

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Lung-related research primarily focuses on etiology and management of diseases. For a variety of reasons, interest in the primary prevention of specific lung diseases has grown, and increasing numbers of observational and experimental studies seek to identify potential areas of intervention. However, primary prevention actually includes two components: (1) health promotion (actions in a population that keep an individual healthy); and (2) disease prevention (specific protective measures against the development of disease or actions taken before the onset of disease that reduce or remove the possibility that

the disease will ever occur). Both activities can be undertaken in the total population or among specifically defined populations. Thus, health promotion efforts acknowledge that “good health” is more than simply the absence of disease.

In current clinical practice, lung health is usually defined as attaining or maintaining lung function (spirometry) or pulmonary exercise capacity that is within 1 to 2 SDs of the population mean for age, sex, height, and weight (1, 2) and being free of lung-related symptoms. This definition accepts that lung function will progressively decline from young adulthood onward (3).

In this article, we challenge the pulmonary community to look for population-based (public health) strategies that not only maximize lung health but also mitigate age-related declines—not only for spirometry but across multiple measures of lung health.

This public health approach has been widely adopted in the fight against cardiovascular disease (4) and is likely to help with the prevention of lung diseases as well (i.e., even small improvements in the average lung health of a population could dramatically reduce lung disease). For example, even small improvements in the lung function of neonates (e.g., through

prenatal interventions) may translate into improvements at full lung growth. In turn, this may have a significant impact on, for example, the incidence of chronic obstructive pulmonary disease (COPD). Although this sequence of events would certainly bolster efforts to improve lung health, we reiterate that the promotion of lung health has intrinsic value, independent of any disease prevention that might follow.

One key to achieving primary prevention goals is to improve our understanding of the complex molecular processes that regulate lung and immune system development and the gradual loss of lung health that often occurs with age. To advance toward these goals, we believe that much could be learned from studying those individuals who are not just free of lung disease but who are doing extremely well. Research on healthy lung functioning will require a new paradigm in which sampling emphasis would shift from diseased individuals (Figure 1, *left*) to oversampling of very healthy individuals (Figure 1, *right*). Figure 1 also highlights the public health perspective that, given the large number of individuals affected, even small shifts at the center of the bell-shaped curve can have important consequences in a population.

For the promotion of lung health, a “life course” approach is very important. Briefly, this conceptual model examines the

long-term effects of diverse exposures across the life span (from gestation to later adult life) and includes biological, behavioral, and psychosocial pathways that operate across an individual’s life course and across generations (5). The life course approach emphasizes two factors: (1) a “critical period,” when an exposure acting during a specific period has lasting or lifelong effects on the structure or function of organs, tissues, and body systems; and (2) “accumulation of risk,” when factors that affect health may accumulate gradually over time. These factors may be separate and independent, clustered (e.g., around poverty), or in “chains of risk” where one exposure or experience tends to lead to another. Although the life course approach has proven helpful in the study of chronic disease (5), it presumes understanding of the natural history of a disease, or, for the current discussion, the normal trajectory of lung health. Unfortunately, we will not be able to obtain the full benefit of the life course approach until we have better measures of lung health (see section “What Are The Potential Measures of Lung Health”) and an improved understanding of their normal trajectory (see section “What Is the ‘Normal’ Trajectory for Lung Health”) over an individual’s life span and possibly across generations.

In this article, we discuss key questions in the area of lung health promotion and briefly summarize the few interventions that have been proposed or studied to date. To stay focused on health promotion, as compared with disease prevention, we have tried to limit our discussion to measures that are either within normal limits or above normal. In the example of spirometry, this would include FVC of 80 to 120% predicted (normal) and greater than 120% predicted (above normal). For other measures of lung health (e.g., novel biomarkers or the lung microbiome), these thresholds are less clearly defined, but we have tried to take the same approach. We conclude with suggestions regarding the most promising future directions for this important, but largely neglected, area of lung research.

Key Questions

How Does One Maximize or Maintain Different Measures of Lung Health?

One approach to health promotion is to maximize bodily functioning, however that is measured. Another approach is to slow the “normal” bodily decline that occurs with aging or in response to common or seemingly normal exposures of modern life. Regarding the lungs, and using the example of FVC, one can easily identify opportunities to promote lung health across the life span (Figure 2).

Maximizing diverse measures of lung health is not as simple to assess as in some other organ systems, such as skeletal muscle health. For skeletal muscle, one can easily show that an intervention, such as regular exercise, makes an individual’s muscles stronger, enhances endurance, improves reactivity, and so forth. It is challenging to think of lungs in this way, especially when spirometry measures are considered normal when they are between 80 to 120% of an average predicted value.

When thinking about how to maximize measures of lung health, the age of a person undoubtedly influences the potential to create change, and it seems likely that the magnitude and importance of changes will vary at different ages. Nevertheless, we begin this discussion with the proposition that lung health promotion is possible in all age groups. Even if it is possible, for example, to boost the “normal” FVC of an individual through specific interventions, we acknowledge uncertainty about the broad

Figure 1. A proposed paradigm shift in research on lung health. Current research tends to oversample individuals at the lower end of the lung health spectrum (however defined). This reflects the current emphasis on understanding disease states, which focuses measurement on either the population norm or on diseased individuals who are compared with the population norm. An alternative approach would be oversampling extremely healthy individuals. The paradigm shift is independent of the measurements undertaken and would apply to all forms of research, whether genomic, proteomic, cellular, physiologic, or patient centered (phenomenologic).

Figure 2. Opportunities to promote lung health. The *solid line* shows normal age-related changes in lung function throughout life (normal curve estimated from data in Reference 12). The *dotted line* demonstrates opportunities to promote lung health: (a) improvements in lung development during the prenatal period and early childhood, (b) strategies to allow maximal lung growth during childhood, and (c) strategies to slow the “normal” age-related loss of lung function during adulthood.

value to creating this change in a seemingly healthy population. For example, although there is longstanding evidence that higher FVC is associated with lower all-cause mortality (6, 7), no study has yet demonstrated that boosting an otherwise normal FVC increases longevity.

Another approach to lung health promotion is to slow the normal decline with aging or in response to common or seemingly normal exposures of modern life. Maintenance of youthful lung measures for a longer time would qualify as health promotion. What makes the lungs of some people more resilient to aging—or to other common exposures that are known to have adverse effects on the lung?

To approach these issues, researchers need a better understanding of how to assess lung health and the normal trajectory of these measures (tests) over time.

What Are the Potential Measures of Lung Health?

Although ideal measures of lung health do not yet exist, it is a useful intellectual exercise to consider what would constitute the ideal. Table 1 shows attributes that could help attain the ideal.

Current clinical practice emphasizes quantification of lung physiology as it relates to disease states. Commonly used tests include pulse oximetry and measurement of arterial blood gases (8–10). Another commonly used test is spirometry, which includes FVC, FEV₁, ratios (e.g., FEV₁/

FVC), and other measurements that may be obtained indirectly (e.g., functional residual capacity, residual volume) (8, 9). A large body of research literature provides normative spirometry data for different populations, such as the general U.S. population (11) and other populations (12). Because of the difficulty of performing spirometry in young children, one technique that is gaining popularity is impulse oscillometry (13), which requires a lower level of patient cooperation than spirometry.

Several other physiologic methods are available, but they are less frequently used. These include measurement of diffusion capacity, quantification of V/Q mismatch (shunt), and other measurements that combine an assessment of cardiac and respiratory physiology. For example, echocardiographic and ECG measurements may be combined with spirometry or quantification of diffusion (8–10).

In general, the clinical literature focuses on the relief of patient symptoms/signs but does not necessarily attempt to quantify a patient’s subjective experience or its relationship to objective measures. For example, a sharp distinction is often drawn between tachypnea (which is quantifiable) and dyspnea (subjective experience of distress or shortness of breath). It is possible to measure FEV₁ before and after administration of bronchodilators, but formal attempts to quantify the relationship in the changes in physiologic measures to

changes in healthy individuals’ subjective experience are rare. Although some integrated measures exist—so called “field exercise tests,” such as the 6-minute walk test or the shuttle walk test—the emphasis remains on quantification of disease states (9). Moreover, commonly used questionnaires in health services research (e.g., the Short Form-36 general health survey [14]) do not directly address lung health; this domain is generally left for disease-specific questionnaires (15–18). An overarching concern is the observation that, in at least some patients, the correlation between improvement in objective measures (e.g., FEV₁ after bronchodilators) and subjective experience (e.g., quality of life) is not strong (19). Many interpret this as a failure of the subjective measure, but another interpretation is that the two measures capture different aspects of lung health. Another concern, particularly with the integrated measures (e.g., 6-minute walk test), is that they were designed to detect and quantify changes below the norm; there is little discrimination between different levels of “normal.”

Newer approaches to quantifying lung function include those that address pulmonary function in novel ways and those that may lead, indirectly, to different paradigms of measurement of lung health. An example of the first approach is aerosol-derived airway morphometry (ADAM), which is of major interest because it is noninvasive and because, unlike conventional techniques like spirometry, it can be used for the detection of not just functional changes but also morphological changes at the level of the small airways (20). The second approach is discussed in two review articles that point out that it is increasingly possible to quantify biochemical markers for aspects of lung health that have, until recently, been inaccessible using conventional methods (21, 22). For example, it is possible to detect genetic and proteomic biomarkers that are associated with lung repair, maintenance and growth of epithelium, remodeling, and regeneration. In this context, one area that has not been studied systematically is that involving the global inflammatory state of the lung and how it relates to remodeling and regeneration. Use of techniques such as the measurement of exhaled nitric oxide (23) in healthy populations has the potential for improving our understanding of lung resiliency.

Table 1. Desirable attributes of measures (tests) of lung health

Attribute	Description and Rationale
Noninvasive	Noninvasiveness will tend to provide data that are closer to actual function and decrease ethical problems for research.
Available for early life	Prior research demonstrates that key aspects of lung health are established early in life. The ability to understand lung health ideally would begin at conception and continue during early childhood.
Calibration	Measures should be calibrated for the “high end” of the spectrum, rather than the population average or the value of individuals with disease. They should also demonstrate good calibration over the age span (i.e., not have either floor or ceiling effects in children or the elderly).
Morphology	Measures should capture morphological aspects (i.e., not just lung volumes but also the structure and function of gas exchange units during normal growth and repair and in response to interventions).
Biochemistry	Measures should be related to biochemical markers (genetic, proteomic, and biochemical indicators of restoration and resiliency) and, if such relationships exist, to the lung microbiome.
Functional status	Measures should be related to objective measures of functional status, including instrumental activities of daily living, and not be limited to only measuring exercise endurance, which depends on intellectual function and cognitive tasks.
Phenomenology	Measures should be related to subjective patient experience, both negative (e.g., the experience of “dyspnea”) as well as positive (e.g., the sensation of being able to take on physically challenging activities, such as sports, or, for children, active play).

Another important area of measurement research that deserves mention, even though it has not yet directly addressed lung health, is the National Institutes of Health–supported effort to improve the measurement of patient-reported data (PROMIS) (24). The PROMIS effort strives to create a set of tools that are free, calibrated to commonly encountered patient populations, and easy to use—both for the patient and for the researcher. The development of such tools for lung health would be a welcome development.

Finally, an emerging area of interest for lung health is the lung microbiome (i.e., the composition of the microbes found in healthy lungs). Historically, healthy lungs were believed to be sterile. However, numerous studies in the past 5 years have identified bacteria in the bronchoalveolar lavage of healthy subjects (25). These include some typically easy-to-culture organisms (e.g., *Streptococcus*) and some difficult-to-culture species (e.g., the

anaerobes *Prevotella* and *Veillonella*). In general, the bacterial load is small, but identifiable, and includes many members of the oral microbiome. Decades ago, it was demonstrated that aspiration of oral microbes is extremely common in healthy individuals (26–28). Furthermore, the air we breathe is not sterile and contains 10^4 to 10^6 bacteria/ m^3 (29). The lungs provide a warm, humid environment composed of numerous microanatomic niches that vary in temperature, oxygen levels, and extracellular nutrients. Barrier and immunologic defenses control the numbers of microbes in the lungs, resulting in an environment that includes various types of transient and persistently colonizing microbes. Although the lung microbiome is very different in nature (and function) from that of the gut, it should be no surprise that the lungs, which are constantly seeded by microbes from the mouth and air, also harbor microorganisms during health.

Unfortunately, the measurement of the lung microbiome presently involves an

invasive procedure, bronchoscopy, thereby limiting the applicability of surveillance or routine measurement of the lung microbiome during health. At present, the major question is whether the lung microbiome during health provides physiologic or immunologic benefit to the individual or whether it is simply a dynamic commensal population that is tolerated, as long as there is no harm to the lungs.

What Is the “Normal” Trajectory for Lung Health?

Lung development. The fetal lung is one of several structures that buds from a primitive tube of foregut endoderm (30). Division of the tube separates the future trachea from the esophagus, whereas the lung distal to the trachea is derived from buds that form from the ventral endoderm beginning in the fourth week of gestation in humans. The bronchi and major branches develop in the first 3 months of fetal growth and, although the development of alveolar units may continue postnatally, branching of the conducting airways does not. This observation is critical for the promotion of lung health in that environmental factors that affect development of the airways *in utero* have the potential to have long-lasting effects over the life course.

Regarding the programming of normal lung development, rodent studies reveal that this programming is provided by the mesenchyme surrounding the endoderm rather than the endodermal cells themselves (22, 30). Soluble factors secreted from the mesenchyme that control lung development have been implicated in the development of lung diseases later in life, including members of the transforming growth factor- β /bone morphogenic protein pathways (implicated in the development of pulmonary fibrosis and pulmonary hypertension, respectively), Wnt pathway members (implicated in lung cancer), and members of the fibroblast growth factor and epithelial growth factor pathways (shown to be protective in some models of lung injury) (22, 30).

Although the healthy adult lung is not sterile (25), fetal lungs are. In the immediate postdelivery period, infant mucosal surfaces are quickly populated by microbes derived from the mother (vaginal and intestinal microbiota in cases of vaginal delivery; skin microbiota in cases of cesarean section) (31). Thus, with their first breaths, neonatal

lungs are exposed to microbes from the air and from the neonatal nasopharynx. The origins of the lung microbiota have not been studied in healthy infants, but a recent longitudinal study of seven infants with cystic fibrosis demonstrated concordance between the microbial communities of the gut and those of the respiratory tract, with evidence of temporal precedence in the gut (32). In germ-free rodents, the lungs have fewer alveolar macrophages, implicating a role for the lung microbiome in regulating alveolar macrophage biology (33, 34). In experimental mouse models, emerging evidence suggests that microbial exposure of the lungs during the neonatal period is also important for developing immunologic regulatory networks. Thus, although much remains to be learned, it seems likely that the composition of the lung microbiome also contributes to early postnatal lung development.

A large alveolar surface area, approximating the size of a tennis court, is required for the normal exchange of oxygen and carbon dioxide. This large surface, which harbors half the blood volume at any given time, is separated from the environment by only a two-cell-thick, delicate membrane and a thin layer of alveolar lining fluid. To meet the challenge of this hostile environment, lung development is accompanied by the development of a finely tuned, tissue-specific immune response (35). Dendritic cells continually sample material in both the airways and alveolar space and present antigens to alveolar macrophages and lymphocytes in the lung and the regional lymph nodes to coordinate an immune response to pathogens. Alveolar macrophages are a long-lived, developmentally distinct, lung-specific monocyte population that plays a key role in both dampening potentially destructive inflammation in response to bland environmental stimuli and coordinating the immune response to pathogens (36). Excessive activation of the immune system or an inadequate immune response to pathogens can result in permanent loss of lung health. Environmental stimuli, particularly exposures during the perinatal period, have been shown to strongly affect the development of mucosal immunity in the lung (37).

Lung development continues through the birthing process, as the secretion of surfactant and differentiation of alveolar type I cells occurs just in time to allow the

switch from the placental circulation to air breathing (22). Although conventional teaching has suggested that alveolarization is nearly complete by age 8 years, with the bulk occurring before age 2 years, investigators have recently challenged this paradigm in careful studies in animal models and in normal humans using helium-3 magnetic resonance imaging (38, 39). The remarkable growth of the lung from infancy to young adulthood has been closely linked to height in both population-based surveys and recent unbiased genetic association studies (11, 40). This growth is attributable to both airspace enlargement and an ongoing process of alveolar generation (38). Although the molecular mechanisms driving alveolar generation in growing children and teens are largely unexplored, a recent study in mice after pneumonectomy suggests that vascular tufts originating from the vasculature signal the differentiation of epithelial progenitor cell populations, a mechanism reminiscent of the mesenchymal-epithelial crosstalk required for lung development (41).

The processes of lung development and lung growth have been strongly linked to environmental factors in epidemiologic studies. For example, both *in utero* exposure and exposure in early childhood to cigarette smoke and environmental pollutants have been associated with impaired lung development in children and young adults (42, 43). Understanding how environmental factors interact with the normal developmental pathways is a very important area for investigation, particularly *in utero* when interventions have the potential to impact lung health in later life.

Lung regeneration. In 2007, Yamanaka and colleagues described a set of four transcription factors, Oct3/4, Sox2, Klf4, and c-myc, that were sufficient to generate pluripotent stem cells from human dermal fibroblasts (44). The discovery of these induced pluripotent stem cells has revolutionized the field of regenerative medicine and spurred the search for progenitor cell populations in the lung. Several groups of investigators have performed careful lineage tracing studies and advanced cell culture techniques to elucidate progenitor cell populations in the lung, and it now appears there are multiple progenitor cell populations that are hierarchically organized from the airway to the alveoli (22). In the airways, basal cells

lacking contact with the airspace can be induced *in vitro* and *in vivo* to form the ciliated airway of the epithelium (45). These cells appear to be the precursors of Clara cells, which can also differentiate into ciliated epithelium and perhaps contribute to more distal airway regeneration (46). The progenitor cell population for the alveolar space has not been definitively identified. The traditional concept that alveolar type II cells proliferate and differentiate into type I cells has been challenged by the finding of potential progenitor populations at the bronchoalveolar duct junctions and the finding of rare cells scattered throughout the alveolar space expressing the integrin $\alpha 4\beta 6$ (47–49).

Identifying putative stem cell populations, combined with advances in tissue culture and engineering, offers the potential to stimulate lung regeneration in ways that were not conceivable even a decade ago. Furthermore, although the goal of driving induced pluripotent stem cells derived from the lung or other tissues toward a lung cell phenotype has not yet been achieved, this technology offers enormous opportunities for the development of lung regenerative therapy and can be used to enhance our understanding of the normal process of lung aging.

Normal aging. The use of age-corrected data to define normal lung function tends to hide the significant loss of lung function associated with aging. According to data from the National Health and Nutrition Examination Survey (NHANES) III study, a 64-inch-tall woman will have an FVC of ~ 3.78 L at age 20 years (11). Even if she maintains her height, she can expect to lose 13% (0.5 L) by age 60 years and 26% by age 75 years. Our understanding of the molecular changes that underlie this normal loss of lung function is very limited. Pathologically, lungs from older individuals show alveolar airspace enlargement and loss of alveolar septae in a pattern reminiscent of emphysema (50). In addition, there is a clear association between age and the risk of developing lung fibrosis (51). Although our understanding of normal aging in the lung is incomplete, active investigations into both the life span and “health span” in cellular systems and model organisms suggest common mechanisms that might be exploited to promote both.

Another area of active research focuses on telomeres, repetitive DNA sequences that cap the ends of chromosomes (52). Each round of cellular replication results in telomere shortening, leading to an age-related reduction in telomere length. When telomeres become critically shortened, they are recognized by DNA damage pathways, activating a cellular program termed senescence (53). Genetic strategies that delay telomere shortening or prevent the development of senescence mitigate aging phenotypes in model organisms (52). Interestingly, mutations in the telomerase reverse transcriptase (TERT) gene, which maintains telomere length, have been associated with the development of pulmonary fibrosis (54). Telomeric shortening is clearly important for rapidly regenerating tissues, including the skin and gut, but it is less clear how it is related to tissues such as the lung, in which cellular turnover is slow (22).

A seemingly unrelated theory suggests that mitochondrial dysfunction plays a causal role in the aging phenotype (55, 56). According to this hypothesis, the age-related accumulation of mitochondrial damage and impairment in biogenesis reduces the metabolic resources for regeneration and increases the levels of mitochondrially derived reactive oxygen species (ROS). These mitochondrial ROS can further damage the mitochondria, resulting in a feed-forward mechanism associated with rapid aging (55). Support for this hypothesis comes from studies showing that environmental factors that accelerate the age-related decline in lung function, for example cigarette smoke and particulate matter air pollution, induce generation of ROS in lung cells (57, 58).

Might these apparently disparate hypotheses be related? Proteins involved in telomere maintenance can be found in mitochondria, where they directly affect mitochondrial respiration and ROS generation (55). In addition, p53, required for the induction of senescence in response to telomeric shortening, can negatively regulate the transcription of *PCG1 α* and *PGC1 β* , which are important regulators of mitochondrial biogenesis (59). Exercise, which may reduce aging phenotypes, activates *PGC1 α* through the master metabolic sensor AMP kinase (60). The synthesis of these data yields a uniform theory of aging that places metabolic factors (including anabolic hormones and

transcription factors such as insulin, insulin-like growth factor-1, and *PGC1 α/β* , and factors that regulate them, including AMPK, p53 and sirtuins) at the center of the aging process (55). These factors promote mitochondrial biogenesis and slow telomere shortening and may thereby delay the aging phenotype. This hypothesis represents a paradigm shift as it explains how altering metabolism through diet, exercise, and weight loss might slow the development of the aging phenotype and suggests pathways that might be manipulated to enhance these effects. Likewise, future research might also focus on why some individuals are unusually resilient to harmful exposures, such as cigarette smoking. The goal of such research would not be to encourage smoking, of course, but rather to learn about mechanisms that might be useful in promoting resilience to common lung insults in otherwise healthy lungs.

Potential Lifestyle and Environmental Interventions

A variety of lifestyle and environmental interventions may promote lung health. In this section, we briefly summarize the interventions that have been proposed or studied to date. In reviewing this literature, we acknowledge the challenge of staying focused on the promotion of lung health as compared with disease prevention. For example, a population-based study that focused on an outcome of FVC less than 80% predicted (yes/no) would be outside our purview, because this outcome is, by definition, abnormal. Even population studies that reported on the full spectrum of FVC values could be problematic if the abnormal result (FVC < 80%) was responsible for an overall association when there actually was none among those in the upper end of the distribution curve (FVC $\geq$ 80%). However, we could not be too strict in our review or there would have been very few articles left for discussion.

Tobacco Smoke

Tobacco smoking, including second-hand exposure, contributes to substantial disease burden worldwide (61). Inhalation of tobacco smoke is common and often unavoidable and, for these reasons, we include it in this discussion of lung health. Tobacco smoke exposure *in utero* and

during early childhood may permanently affect the developing lung, including increased risks of respiratory illness and reduced lung growth (62, 63). In healthy adults, cigarette smoking is linked to increased respiratory symptoms, including cough, dyspnea, or wheeze (64), and has established chronic adverse effects on lung health, including acceleration of age-related decline in lung function (65, 66).

Smoking cessation is one of the only interventions that has been shown to alter the trajectory of lung function decline over time (67). In addition, both smoking cessation and smoking reduction have been shown to reduce self-reported symptoms of cough and phlegm in a general population (68). A recent systematic review shows consistent evidence that smoking bans reduce exposure to second-hand smoke in workplaces, restaurants, pubs, and public places (69). In 2004, the Irish government introduced the world's first comprehensive national legislation banning smoking in all workplaces, and investigators reported an 83% reduction in particulate matter (PM) and an 80% reduction in benzene concentrations after the ban; moreover, nonsmoking workers reported a significant decrease in self-reported cough and phlegm after the ban (70).

Indoor Air

An estimated 3 billion people, often women and children, are exposed to smoke from biomass fuel and coal used for cooking and heating and from kerosene used for lighting (71). Although evidence on the health effects of regular exposure to biomass-related indoor air pollution remains sparse, the available evidence points to these exposures being associated with increased lower respiratory infections and reduced lung growth in children and an accelerated decline in lung function and chronic airflow obstruction in adults (72). These exposures may also affect lung growth and development *in utero*. In developed countries, the particulate exposures that occur in most houses that heat with open fireplaces probably have adverse respiratory effects in individuals with chronic lung disease (73), but the magnitude of these effects is unknown. Given the likely worldwide effect of indoor air pollution on lung health, there is a major push to improve cook stoves and to do research to more accurately understand, and ultimately decrease, the risk.

Nitrogen dioxide (NO₂) is another common indoor air pollutant, often related to the use of gas stoves and gas furnaces (74). Although studies support adverse effects of NO₂ on respiratory health in individuals with asthma (74, 75), and exposure to NO₂ in experimental studies leads to airway inflammation in healthy volunteers (76), studies of the respiratory effects of NO₂ on healthy lungs have been inconsistent. For example, some studies suggest that early exposure to indoor NO₂ is associated with increased respiratory symptoms and lower respiratory illness (77, 78), whereas other studies have shown no adverse effects of NO₂ on otherwise healthy infants (79, 80).

Relatively few randomized controlled trials (RCTs) have investigated the effectiveness of strategies aimed at improving indoor air quality. For example, the placement of high-efficiency particulate air cleaners in the indoor environment may reduce PM concentrations by 30 to 60%, with a subsequent decrease in systemic inflammation, even in healthy volunteers (81). Only few intervention studies have investigated strategies aimed at decreasing indoor NO₂ concentrations in homes or at schools (82–84). A cluster-randomized, double-blind, crossover trial in 400 Australian students showed that the use of flued instead of unflued gas heaters was associated with a decrease in cough and wheeze but had no effect on lung function (84). RCTs are needed to determine whether improving indoor air quality has long-term beneficial effects on lung health.

Outdoor Air

Outdoor air pollutants, including but not limited to PM, NO₂, ozone, and sulfur dioxide, have been shown to have both acute and chronic consequences on lung health. For example, daily fluctuations in PM concentrations have been associated with decrements in peak flow rates in normal children and acute respiratory hospital admissions in children leading to school absences. Furthermore, longitudinal general population studies in children suggest that PM exposure is associated with impaired lung function growth (42). In addition to possible adverse effects on the maximal attained lung function, results from epidemiological studies suggest a significant association between PM concentrations and the rate of age-related decline in FEV₁ (85). Elevated ozone

concentrations, occurring in urban areas of the United States, have been associated with respiratory symptoms and reversible decrements in lung function among healthy individuals, especially among those exercising outdoors (86). Although ozone exposure also has been associated with airway inflammation (87), the chronic effects of ozone exposure on the lung remain unclear (86).

Reducing ambient pollution exposure may have major benefits to lung health. For example, after the reunification in Germany in 1990, Eastern Germany noted a significant decline in the levels of sulfur dioxide and total suspended particulates, with a subsequent decrease in bronchitis and frequency of colds and respiratory symptoms in children (88). Similarly, reductions in particulate levels in Switzerland over an 11-year follow-up period had a beneficial effect on respiratory symptoms among adults (89). Importantly, decreasing exposure to airborne particulates appears to have long-term benefits by attenuating the decline in lung function (85). Further studies are needed to better understand the health impact of different fractions of PM, and to determine whether there are optimal pollutant concentrations below which adverse effects on lung health are minimized or eliminated. Also, as noted previously, there is value in studying individuals who are exposed to common pollutants but who do not develop adverse effects; what explains their resilience to the lung insult? Could this improved understanding guide the development of interventions to promote resilience in others?

Acute Respiratory Infections

Acute respiratory infections (ARIs) are an almost inevitable part of human existence, particularly in children (90). The long-term effects of lower and upper respiratory infections are probably different, as are the sequelae of different viruses (and subtypes of viruses) that affect the respiratory tract. For many years, both animal and human studies have suggested that specific lower respiratory pathogens (e.g., respiratory syncytial virus) have adverse effects on lung development in seemingly healthy individuals (91). For example, animal models of viral infection during lung development suggest that specific developmental factors are important in determining the consequences of infection

on long-term lung function. Although the precise mechanisms remain under investigation, inflammatory mediators induced by viral infection are believed to affect the remodeling process and provide a biologically plausible mechanism for impaired spirometry. The impact of ARIs on all other measures of lung health (e.g., the lung microbiome) is largely unknown.

Vaccines provide a potential intervention to reduce frequency of ARIs and their likely adverse effects on lung health maximization and maintenance. For example, if specific types of respiratory infections (e.g., respiratory syncytial virus, human rhinovirus) are linked with suboptimal lung health, one might vaccinate individuals against these viruses and thereby promote their lung health. To date, such trials have not been done. Likewise, what factors make individuals more or less susceptible to ARIs? Also, as discussed earlier with respect to smoking and pollutants, studying individuals who contract ARIs and do not develop problems might also be valuable: what accounts for their resilience?

Nutrition

Many studies have examined the potential role of nutritional factors in the primary prevention of specific lung diseases, especially asthma and COPD. Less is known about the effect of nutrition on the maximization or maintenance of lung health, including at what point in the life course nutritional factors may be most influential. To date, data are mostly from observational studies of general adult populations, in which investigators examine the association between the intake or serum level of individual nutrients (or overall dietary patterns) and limited markers of lung health, usually FEV₁ or FVC. Randomized trials of micronutrient supplements are uncommon but available.

Observational studies of individual nutrients. Epidemiological studies of nutrient intake in adult populations suggest that higher intakes of certain micronutrients are associated with better lung function. For example, a study of 6,555 Dutch adults found a positive association between higher intake of certain micronutrients (β-carotene and vitamin C) and FEV₁ and FVC (92). Similar results for carotenes, vitamin C, and vitamin E were shown in population-based studies in Nottingham (93), China (94), and Italy (95). Likewise, an analysis of

nationally representative U.S. data in 2000 found that higher intakes of specific antioxidants (total carotenes, vitamin C, and vitamin E) were positively associated with FEV₁ (96). Additionally, a 2001 analysis from Scotland demonstrated a positive association between antioxidant intake (β -carotene and vitamin C) and FEV₁ (97). Although there is some consistency across these cross-sectional studies, the magnitude of the associations was usually small, and residual confounding (e.g., by socioeconomic status) remains a plausible explanation. Moreover, the age at which a specific nutrient may have influenced lung health is not clear.

Publications with longitudinal data are sparse. For example, dietary intake and FEV₁ were measured in a cross-sectional study of 2,633 adults, with repeat measures 9 years later in 1,346 of the subjects. Decline in FEV₁ was lowest among those with higher average vitamin C intake (i.e., 51 ml less decline for each 100 mg of vitamin C consumed per day) (98). Longitudinal studies have also shown less smoking-related decline in FEV₁ over 4 years among those with higher vitamin C intake (99). Although smoking cessation remains the most important intervention for lung health promotion, the possibility of a mitigating benefit from vitamin C could have implications for adults who are unable to quit and others, such as children, who are regularly exposed to second-hand smoke.

In addition to levels of nutrient intake, serum levels of various nutrients have been used to examine the association between nutritional factors and lung health. Nationally representative data in the United States found that higher serum levels of vitamin A, β -cryptoxanthin, vitamin C, and vitamin E were associated with higher FEV₁ (100). Another cross-sectional study demonstrated that subjects with the lowest serum values for β -carotene, β -cryptoxanthin, lutein, vitamin C, and vitamin E had the lowest values for FEV₁ and FVC (101). Serum carotene levels also have been associated with greater lung function in both community-dwelling and disabled populations (102–104). Low serum levels of 25-hydroxyvitamin D also have been associated with lower lung function (105). The causality of these associations is unclear. Longitudinal data on serum nutrient concentrations and lung function in the general population are lacking.

Randomized trials of micronutrient supplements. Another body of research has focused on actual interventions using micronutrient supplements. As one might expect, supplementation of chronically malnourished individuals has positive health effects. For example, a 2010 study conducted in a cohort of 1,371 Nepali children, age 9 to 13 years, whose mothers had been randomized to receive vitamin A supplementation during pregnancy, had higher FEV₁ and FVC than children whose mothers received β -carotene or placebo (106). Although this demonstrates the importance of correcting micronutrient deficiencies in chronically malnourished populations, the generalizability of these results to the U.S. population is unclear.

There are very few RCTs of micronutrient supplementation and lung health in well-nourished populations. In one RCT, adults at high risk for cardiovascular events received daily antioxidant vitamins for 5 years (vitamin E 600 mg, vitamin C 250 mg, β -carotene 20 mg) and the

intervention had no effect on lung function (107). Another large RCT showed a significantly higher incidence of lung cancer in current smokers supplemented with 20 mg/d of β -carotene for 5 to 8 years (108). On a more positive note, some RCTs have shown protective effects of antioxidant supplementation on lung function among individuals with pollutant exposures, such as ozone (109, 110). Similarly, a recent RCT found that vitamin C supplementation during pregnancy improved pulmonary function among newborns of smoking women, particularly among women with genotypes associated with smoking-related lung disease and addiction (111). Thus, micronutrient supplementation may promote lung health during specific periods, such as gestation, and in specific high-risk populations.

Observational studies of dietary patterns. Another approach to evaluating the role of diet on lung function is to examine overall diet, as opposed to intake of a single nutrient. As most nutrients function

Table 2. Future research recommendations regarding measures of lung health

Formal quantification of the relationship between “hard” measures (e.g., impulse oscillometry, exhaled nitric oxide) and “soft” measures (e.g., PROMIS-like questionnaires on subjective experiences, such as dyspnea or excellent lung function). Given the current emphasis on patient-centered measures, it is important to assess the concordance (or discordance) between functional and phenomenological measures and more exact physiological measures. At the “high end,” it is also important to assess what factors *outside the measurement focus* are strongly associated with concordance (e.g., if one is measuring FVC and subjective experience, how is this relationship affected by socioeconomic status?).

Statistical assessment of new sampling strategies. Given limited resources, if we are to study the best possible degree of lung functioning, it is going to be important to oversample individuals in the healthy end of the spectrum (see Figure 1). The following statistical issues would need to be formally assessed:

- Unlike patients with severe lung disease, whose lung function tends to oscillate around a downwardly sloping line, individuals at the high end may have a wider degree of oscillation around a line with a less steep slope; consequently, the stability of estimates of lung function (whatever they may be) will be different, and it will be necessary to address not just the issue of how sampling fractions affect point estimates but also how sampling fractions affect trajectories.
- A similar problem is likely to occur when one measures resiliency, in that very healthy lungs may “climb a steeper recovery curve”; this will also affect how one addresses oversampling issues.

Continued work on improving techniques and acceptability of physiologic tests in infants and children. Infancy and childhood have a critical impact on lung development, but many tests are still difficult to conduct in this age range. Additional research is needed to make physiologic tests more acceptable to this population and then correlate these tests to both old and new measures. Such research may need to include animal studies.

Statistical assessment of the correlation between genomic/proteomic markers and physiologic tests, particularly in the context of oversampling.

Research on the psychology of participation in studies by individuals in the upper (healthier) end of lung functioning. Current recruitment strategies tend to focus on diseased individuals who have some perception of possible gain when they participate in research. However, healthy individuals may have very different attitudes to being studied, and it is important to identify how they could be brought into the research arena.

Definition of abbreviation: PROMIS = Patient Reported Outcomes Measurement Information System.

synergistically, looking at the effect of singular nutrients may be an oversimplification. Observational studies of population samples have shown that adults following a “prudent” diet (high in fruit, vegetables, oily fish, and whole-grain cereals) also have higher FEV₁ (112, 113). In a 5-year longitudinal study of the association between dietary patterns and lung function, investigators categorized diets as “traditional” (higher intakes of meat and potatoes, lower intake of soy and cereal), “cosmopolitan” (higher intake of chicken, fish, and vegetables), and “refined foods” (higher intakes of mayonnaise, salty snacks, candy, high-sugar beverages, white bread) (114); they found that the traditional diet was associated with lower FEV₁, and the highest quintile of the refined food diet had a significantly greater decline in lung function over 5 years when compared with the lowest quintile of the refined food diet. Intake of fruit has been associated with FEV₁ in general adult populations in Scotland (115), Netherlands, Finland, and Italy (95), and in 8- to 11-year-old children (116). Longitudinal changes in fruit intake also has been shown to be positively associated with changes in FEV₁ (117), but RCT evidence is lacking.

Physical Activity

Although many studies are available about the impact of physical activity on measures of lung function in patients with lung disease (118–120), few studies have examined the relation of physical activity with lung health measures in a healthy population. In one cross-sectional study, higher levels of physical activity were associated with higher FEV₁ and FVC in 9- to 10-year-old children (121). Another study found that children who were more active from ages 11 to 15 years had better lung function parameters at age 15 (122). Likewise, longitudinal data from Amsterdam found that changes in physical activity over time were positively correlated with changes in FVC in subjects 13 to 27 years of age (123).

In recent years, there has been speculation that swimming may improve lung function. A cross-sectional study of healthy competitive swimmers aged 7 to 19 years found that FVC increased more than would be expected with age, and FEV₁/FVC ratio decreased with age (124). Although this may suggest that swimmers develop large lungs, it also is possible that subjects

with larger lung volumes prefer to engage in swimming rather than other activities. However, another longitudinal study found that the intensity of recreational swimming among 7- to 10-year-old children was positively associated with FVC increase with age (125). Moreover, a recent letter presented the case of a competitive freediver who repeatedly used a technique designed to enhance athletic performance and showed increases in lung volumes over time. Taken together, these data support the hypothesis that certain techniques and exercises may alter respiratory system mechanics (126). Although these favorable findings could be due to increased upper body musculature and not structural changes in the lung *per se*, they do represent an improvement and are worthy of further study.

Few (if any) population-based studies have examined the association between physical activity and lung health in a general population of healthy adults. Likewise, we

are not aware of longitudinal studies on how physical activity affects lung function over time.

Overweight and Obesity

Both body mass index (BMI) and waist circumference (WC) are associated with lung function in the general population (127). Increasing BMI and weight gain in adults has been associated with decreases in lung function; however, there is evidence of a U-shaped relationship, and studies that assume linearity may misrepresent the association (128, 129). Cross-sectional studies have shown that WC and waist-to-hip ratio also are associated with lung function in normal-weight, overweight, and obese adults (130, 131), suggesting that distribution of fat may be important. Longitudinal evaluation of age-related changes in lung function among healthy young adults found that FEV₁ and FVC decrease both with higher baseline BMI and with increasing BMI over time, and that

Table 3. Future research recommendations regarding the normal trajectory of lung health

Goal	Future Research Recommendations
Promote Lung Development and Growth	<p>Investigate the mechanisms by which environmental stimuli affect lung development, with a focus on the interrelations between the environment and lung proteostasis, epigenetic changes, and genetic risk factors.</p> <p>Investigate the development of the immune response in the lung, including a better understanding of the mechanisms for distinguishing between environmental threats and contaminants (e.g., the role of the microbiome in this response).</p> <p>Investigate the biology of lung growth during gestation and childhood and the impact of environmental stimuli on these biological factors.</p> <p>Investigate whether development of the immune system in the lung is linked to lung growth and how changes in the environment (including the microbiome) might affect these processes.</p> <p>Investigate how interventions targeting other organ systems (e.g. exercise, nutrition) affect mechanisms of lung development.</p>
Maintain Lung Functioning	<p>Investigate the mechanisms of aging in the normal lung and determine how environmental and genetic factors (and gene–environment interactions) might contribute to the aging phenotype.</p> <p>Investigate whether developmental pathways can be reactivated during adulthood to promote lung regeneration.</p> <p>Investigate “resilience factors” that are associated with absence of serious disease in some smokers, particularly heavy smokers.</p>

those subjects who reduced their BMI also increased their lung function (129, 132). The relationship between BMI, WC, and lung function is seen more consistently in adults than in children. In contrast to the adult literature, pediatric studies often find no relationship between BMI and WC and lung function, or the association is positive (predominantly in the lower part of the BMI and WC distributions) (133).

Future Research

There is an urgent need for research on lung health promotion as an essential part of any primary prevention initiative. We conclude with suggestions regarding the most promising directions for future research.

Measures of Lung Health

Although the current literature is primarily focused on lung disease, most of the current measures of lung health could be adapted to the study of the healthy and extra-healthy and so get us closer to the ideal expressed in Table 1. Furthermore, it would be helpful to delineate a more health-oriented research strategy that would include the development of new measures (Table 2). Both old and new measures would contribute to a lung health “panel” that would provide a more complete picture of the lung health of an individual or population.

One way to implement such a strategy would be to use existing measures but focus them on different population subsets. Thus, instead of measuring lung functioning on a representative sample (so as to establish norms and prevalence of disease), it would be important to target healthy and very healthy individuals from either new or existing cohorts (Figure 1). Over time, this could lead to an expanded database on the healthy end of the spectrum. In addition, such a research program should be combined with the development of patient-centric questionnaires that address those areas of lung health that are currently considered “subjective.” For example, if the PROMIS tools can include measurement of anger, it seems reasonable that one could measure how very healthy people experience respiration. Last, in an era in which increasing numbers of genomic, proteomic, and biochemical markers are becoming available, it would be desirable to

oversample patients who have demonstrated resiliency to lung insults.

Normal Trajectory of Lung Health

Available data support the hypothesis that one can promote lung health over the life span (Figure 2). To test this hypothesis, researchers will need to develop interventions that will enhance lung development in the prenatal period, promote the development of lung health during childhood, or slow the “normal” age-related decline in diverse measures of lung health. The development of these interventions will require a better understanding of the basic biology of lung development, growth, and aging. The impact of environmental stimuli and their interaction with genetic, epigenetic, and

proteostasis-related changes in the developing and adult lung is incompletely understood and represents a fertile area for future investigation. The hypothesis that regulation of the immune response in the lung by the respiratory microbiome might promote healthier lung development also merits study. Likewise, the impact of interventions targeted at organs outside the lung (e.g., weight loss among the obese) provides opportunity to assess impact of intervention (see Potential Interventions, below) but also the underlying biologic mechanisms. Finally, an overarching recommendation is to study the exceptions to the rule (i.e., those individuals who do not experience adverse consequences to exposure to smoke, pollution, ARIs, and other adverse factors); what are these

Table 4. Future research recommendations regarding potential interventions targeting lung health

Intervention	Future Research Recommendations
Tobacco smoke	Determine whether there are critical periods of exposure when smoking avoidance would have maximum benefit to improve lung health.
Indoor air	Identify potential thresholds, if they exist, that result in adverse or beneficial effects on lung functioning in healthy individuals. Determine the importance of interactions between exposure to multiple common pollutants on lung health.
Acute respiratory infections	Establish the effect of acute respiratory infections on diverse measures of lung health at different points in life span. Develop vaccines or other interventions to prevent or mitigate the effects of the most damaging respiratory pathogens. Perform randomized controlled trials of vaccines or other interventions to investigate their effectiveness in preventing acute respiratory infections and their sequelae.
Nutrition	Test the thresholds of nutrient parameters (dietary and supplement intake, serum levels) that results in measureable improvement in lung functioning in healthy individuals. Determine the role nutrition plays in modifying potential decline in lung health due to risk factors such as age, smoking, and genetics. Evaluate the synergistic interaction of nutrients through studies that evaluate overall diet intake.
Physical activity	Establish the effect physical activity has on measures of lung health in healthy individuals. Quantify the amount and type of physical activity resulting in measureable changes in lung functioning in healthy individuals.
Overweight and obesity	Determine the relationship between body habitus and measures of lung health in different populations, at different points in the life cycle. Determine if a change in body habitus results in a corresponding change in lung functioning in healthy individuals.

resilience factors? These recommendations and others are summarized in Table 3.

Potential Interventions

Table 4 summarizes our research recommendations regarding potential interventions to promote lung health. An overarching recommendation is the importance of determining if the effect of an intervention to maximize or maintain lung health is the same at different points in the life course or if there is a critical window to improve lung health. Furthermore, each of the specific interventions requires investigation to determine if the intervention should be applied to the entire population or to specific groups of seemingly healthy individuals.

Clearly, smoking cessation and second-hand smoke avoidance are advised. However, whether there is a critical time in lung development during which smoking avoidance strategies are most effective remains largely unknown. In addition, RCTs show the effectiveness of high-efficiency particulate air cleaners at reducing indoor PM concentrations, but whether these reductions lead to improvements in lung

health in individuals without underlying chronic lung disease also remains largely unknown. In addition, understanding multipollutant effects and whether multipollutant reduction strategies demonstrate increased effectiveness at improving lung health should be prioritized.

ARIs are common and are likely to affect long-term lung health, but data remain sparse. Most research to date has been done regarding future risk of asthma and COPD. Accordingly, there is an urgent need to establish the effect of ARIs on diverse measures of lung health at different points in the life span. Likewise, if adverse effects are confirmed, it would be helpful to develop and test vaccines (or other interventions) that aim to avoid ARIs and thereby avoid the putative adverse impact of these infections.

Although nutritional factors, physical activity, and body weight have been implicated as possible factors affecting spirometry, the currently available literature has important limitations. For example, most research on the role of these factors on spirometry in healthy individuals has been conducted in adults; sparse data are available for infants, children, and

adolescents, or ethnic minorities. Moreover, the data are primarily observational and cross-sectional, not longitudinal. The populations used for this epidemiological research make it difficult to sort out if the interventions would be effective in healthy individuals, as the research probably includes individuals with varying degrees of impaired lung function. Last, we believe that future longitudinal research describing the impact of early life exposures on diverse lung measures will be crucial for identifying if there are “critical periods” for interventions that aim to improve lung health.

Taken together, there are numerous RCTs that would advance the nascent field of lung health promotion. However, in view of resource limitations, we recommend that the most promising populations for these trials are pregnant women and young children. ■

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