Special Communication

Prenatal and Perinatal Determinants of Lung Health and Disease in Early Life
A National Heart, Lung, and Blood Institute Workshop Report

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Human lung growth and development begins with preconception exposures and continues through conception and childhood into early adulthood. Numerous environmental exposures (both positive and negative) can affect lung health and disease throughout life. Infant lung health correlates with adult lung function, but significant knowledge gaps exist regarding the influence of preconception, perinatal, and postnatal exposures on general lung health throughout life. On October 1 and 2, 2015, the National Heart, Lung, and Blood Institute convened a group of extramural investigators to develop their recommendations for the direction(s) for future research in prenatal and perinatal determinants of lung health and disease in early life and to identify opportunities for scientific advancement. They identified that future investigations will need not only to examine abnormal lung development, but also to use developing technology and resources to better define normal and/or enhanced lung health. Birth cohort studies offer key opportunities to capture the important influence of preconception and obstetric risk factors on lung health, development, and disease. These studies should include well-characterized obstetrical data and comprehensive plans for prospective follow-up. The importance of continued basic science, translational, and animal studies for providing mechanisms to explain causality using new methods cannot be overemphasized. Multidisciplinary approaches involving obstetricians, neonatologists, pediatric and adult pulmonologists, and basic scientists should be encouraged to design and conduct comprehensive and impactful research on the early stages of normal and abnormal human lung growth that influence adult outcome.

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Multiple influences on human lung growth and development occur, beginning with preconception exposures and continuing through conception and childhood into early adulthood (**Figure**). Numerous environmental exposures (both positive and negative) accumulate along this pathway, and their sum determines lung health and disease. Many studies of perinatal and pediatric lung health and disease have focused on very premature neonates, a population most likely to have aberrant physiology, acute lung injury, or other medical comorbidities in addition to long-term lung disease. However, there is a great need to better delineate the normal trajectories of lung growth and development throughout the lifespan among most infants who are delivered at term or late preterm and to identify the environmental influences that may positively or negatively affect lung development. Although evidence suggests correlations between infant lung health and adult lung function, significant knowledge gaps exist regarding the influence of the preconception, perinatal, and postnatal periods on general lung health throughout life.[1]
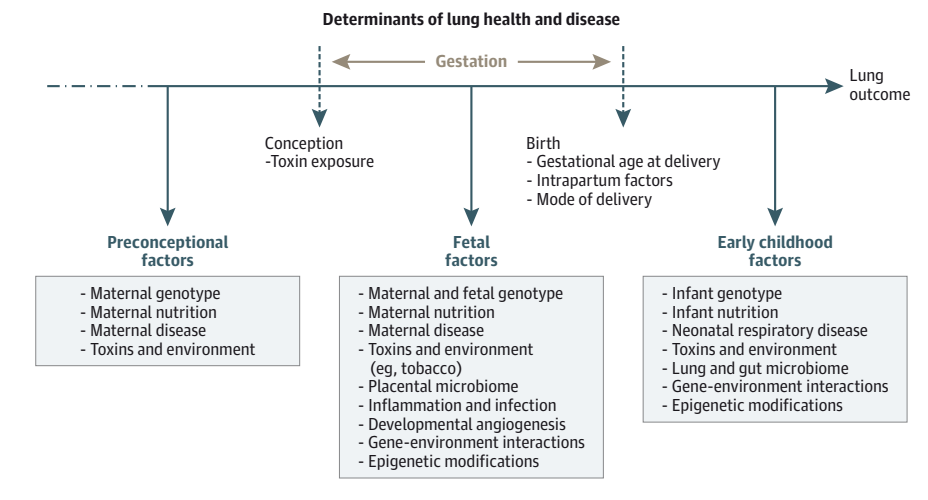
On October 1 and 2, 2015, the National Heart, Lung, and Blood Institute convened a group of extramural investigators to develop recommendations for the direction(s) of future research in prenatal and perinatal determinants of lung health and disease in early life

and to identify opportunities for scientific advancement. Workshop participants were divided into working groups that focused on 4 areas of lung development research: (1) lung development and function in infants that influence the trajectory to health and disease; (2) pregnancy abnormalities that disturb lung development; (3) preconception, prenatal, and postnatal developmental programming; and (4) maternal, fetal, infant, and childhood environmental exposures. Each subgroup reviewed the current state of the science, identified gaps in knowledge, and offered specific recommendations for future research. This report provides a summary of the workshop participants' discussion and recommendations as well as the priorities they identified for future research in prenatal and perinatal influences on lung growth and development (**Table**).

Lung Development and Function in Infants

Normal lung development consists of a series of carefully orchestrated events. Longitudinal studies of lung development and function indicate that, in most cases, an individual's pulmonary function follows a predictable progression from birth through childhood and early adulthood until full maturation at age 22 years.[1-3] Subsequent

Figure. Preconceptional, Fetal, and Early Childhood Factors That Influence Lung Growth and Development

Determinants of lung health and disease

Gestation

Lung outcome

Conception
-Toxin exposure

Birth
- Gestational age at delivery
- Intrapartum factors
- Mode of delivery

Preconceptional factors
- Maternal genotype
- Maternal nutrition
- Maternal disease
- Toxins and environment

Fetal factors
- Maternal and fetal genotype
- Maternal nutrition
- Maternal disease
- Toxins and environment
  (eg, tobacco)
- Placental microbiome
- Inflammation and infection
- Developmental angiogenesis
- Gene-environment interactions
- Epigenetic modifications

Early childhood factors
- Infant genotype
- Infant nutrition
- Neonatal respiratory disease
- Toxins and environment
- Lung and gut microbiome
- Gene-environment interactions
- Epigenetic modifications

gradual age-related declines also generally follow a predictable pattern.[3] Those individuals who begin in the lowest quartile of lung function as an infant are typically in the lowest quartile of lung function as an adult.[1] Individuals in the lower quartile are most susceptible to lung-related disease later in life, probably because of a failure to achieve maximum adult airflow and vital capacity, resulting in premature loss of the physiological respiratory reserves.[2,3] Lange et al[3] reported that diminished airway function (a forced expiratory volume in the first second of expiration <80% predicted) after birth was associated with adult respiratory disease and that accelerated lung function decline (loss of forced expiratory volume in the first second of expiration) later in life was not a required feature of chronic obstructive pulmonary disease. However, multiple aspects of normal lung development, including developmental trajectories, are poorly understood and could be informed by well-designed longitudinal cohort studies.

Furthermore, any adverse exposures prior to or during development (prenatal, postnatal, childhood, and/or adolescence) have the potential to change the trajectory of lung development as well as the loss of lung function with age.[3] The best-studied example is infection.[4,5] Lower respiratory illness in early life has been associated with diminished airway function during early life and, subsequently, an increased risk of chronic obstructive pulmonary disease in late adult life.[6] Even 1 episode of a pediatric respiratory illness (eg, pneumonia or respiratory syncytial virus) may decrease levels of lung function, affect the long-term developmental trajectory, and increase the susceptibility to obstructive lung disease and other complications as an adult.[4,5] Again, preconceptional and early life studies in selected populations are needed to identify the early life modifiers that affect initial lung health trajectories and mediate disease susceptibility.

Techniques for noninvasive longitudinal measurement of airway anatomy and lung mechanics are needed to best evaluate the stimuli and insults that affect initial and long-term trajectories of lung health and disease. Evaluation of neonatal lung function has been challenging because conventional pulmonary function tests (spirometry and plethysmography), imaging methods (chest radiographs, scintigraphy, and computed tomography), and more spe-

cific measures (diffusing capacity of the lungs for carbon monoxide, multiple breath washout, and lung clearance index) provide limited information about spatial heterogeneity of lung disease and require either sedation or ionizing radiation. Newer, noninvasive imaging techniques, such as functional lung imaging with magnetic resonance imaging, are more sensitive to regional changes within the lung parenchyma and may provide quantitative information about both normal and abnormal lung structure and function.[7,8] Functional lung imaging with magnetic resonance imaging has several advantages; it is safe, requires no ionizing radiation, and provides a detailed spatial and temporal resolution to evaluate lung anatomy (airways and parenchyma) and function (regional delivery of gas or blood) using gas agents. Functional lung imaging could be used for longitudinal studies of growth and development of the parenchyma and airways.[7,8]

Dynamic molecular analyses of the human lung are limited by tissue availability, but developmental studies using lung tissue when available and animal models have implemented lung mapping to identify complex networks of genes and transcriptional factors that mediate cell differentiation during lung morphogenesis, injury, and repair[9] (see also http://lungmap.org). In the future, these (and other) novel imaging techniques may provide an approach to better understand the function of individual cells within lung tissue, examine specific functions of these cells, including gene expression, and determine the influence of exposures (eg, antenatal corticosteroids) at the cellular level.

Pregnancy Abnormalities That Disturb Lung Development

Although neonates born very preterm before 34 weeks have the highest likelihood of developing respiratory morbidity after birth, these very preterm infants represent only a small fraction of all babies cared for in neonatal intensive care units annually in the United States. Neonates born early term (37-38 weeks' gestation) or late preterm (34-36 weeks' gestation) represent the largest proportion of babies in neonatal intensive care units. These infants have a significantly higher

Table. Current Challenges, Research Opportunities, and Priorities Grouped by the 4 Major Focus Areas From the National Heart, Lung, and Blood Institute Workshop

Section/Focus Area	Key Barriers and Challenges	Research Opportunities and Priorities
Lung development and function	Absence of standard measures for normative trajectories of lung health throughout development. Need to better understand the prenatal and early postnatal stimuli and insults during critical periods of lung development that affect adult lung structure and physiology. Lack of clinically applicable noninvasive technologies to regionally assess and longitudinally track lung function and pulmonary vascular development from birth through early adulthood.	Define healthy lung structure and function from infancy through early adulthood in highly selected and well-characterized populations. Use preconception cohort studies to identify early life stimuli and insults that affect initial lung health and delineate the physiological and structural changes to the developing lung in early adulthood. Develop noninvasive, clinically applicable imaging techniques to longitudinally assess anatomical, physiological, and molecular respiratory mechanisms in utero and early postnatal life that can also be evaluated through early adulthood. Specific examples include magnetic resonance–based techniques and molecular lung mapping.
Pregnancy abnormalities that disturb lung development	Imperfect and sometimes inconsistent definitions of obstetric phenotypes. Numerous confounding factors that influence postnatal disease including maternal medical disease; fetal sex and race/ethnicity must be considered. Inaccessibility of fetal and neonatal lung tissues for direct sampling and study.	Associate lung outcomes with obstetric determinants (maternal and/or obstetric complications) as well as gestational age or birth weight. Clearly define gestational age and fetal growth restriction. Better characterize the specific obstetric indications for dealing with neonatal pulmonary morbidities, in part by developing prebirth cohorts that detail obstetric phenotypes. Evaluate chronic lung disease throughout life based on delivery indication and factors present during pregnancy and/or at the time of delivery. Determine whether decline in lung function with age is influenced by early term or late preterm birth or specific fetal exposures. Advance the use of fetal lung imaging by magnetic resonance imaging and ultrasonography to assess pulmonary maturity. Evaluate the role of the placenta in pregnancy complications, which may affect fetal lung function. Develop surrogate markers for fetal/neonatal lung injury.
Developmental programming of lung	Lack of information about the role of fetal and early childhood lung microbiome and little understanding of the modifiers that may affect disease. Unknown effect of other tissues or organ systems on lung development. Lack of clinically relevant longitudinal biomarkers of fetal and early childhood lung health. Limited understanding of how in utero and postnatal nutritional environments affect lung development or what the ideal nutritional environment should be to optimize outcomes.	Delineate the association between maternal, fetal, and placental immunity, including the role of the fetal microbiome in normal and abnormal lung development. Discover biomarkers (from maternal blood, amniotic fluid, and/or cord blood) to serve as proxies for fetal lung growth and/or development and identify crucial windows of immune development or microbial exposure. Investigate the influence of the intestinal microbiome on host responses for establishing lung health and disease. Optimize maternal nutrition to properly modulate healthy lung development and mediate disease susceptibility.
Environmental interactions and exposures (maternal, fetal, and infant)	Limited understanding of the mechanisms by which environmental exposures cause injury and alter phenotypes in some individuals. Unknown influence of the airway microbiome during development. Uncertain information regarding optimal vitamin dosage, source, form, and timing of supplementation. Limited tissue availability to examine underlying genetic and molecular mechanisms.	Determine the ideal regimen of vitamin supplementation to reduce the risk of asthma and other adverse early childhood lung outcomes among those at highest risk (eg, offspring of smokers and late preterm infants). Investigate the role of epigenetic modification in mediating effects of nicotine, air pollution, and other environmental toxins. Determine whether epigenetic changes can be reprogrammed after birth to correct, alter, or compensate for fetal lung programming in response to environmental exposures. Evaluate the effects of increasingly available maternal products (eg, electronic cigarettes and marijuana) on the developing lung.

incidence of almost all adverse respiratory morbidities (including respiratory distress syndrome, transient tachypnea of the newborn, pneumonia, respiratory failure, need for surfactant, and mechanical ventilation) compared with those born at 39 weeks and beyond.[10] Todisco et al[11] assessed lung function at a mean age of 12.5 years among former late preterm children (none of whom had respiratory morbidity at birth) and found decreased lung function compared with matched siblings delivered at term, suggesting that differences persist at least into childhood. Recent efforts focused on obstetric quality improvement have resulted in a significant shift in delivery gestational age at or beyond 39 weeks' gestation.[12] Even so, many term and preterm neonates experience respiratory morbidities that are difficult to predict, and many may eventually develop respiratory morbidities later in childhood and as adults.

Increasingly, researchers and clinicians are appreciating that some of this variation in outcome may be explained by the intrauterine environment and delivery conditions, even when delivery occurs at full term. Specifically, whether the delivery is indicated (eg, an induction for maternal reasons such as preeclampsia) or spontaneous (eg, due to onset of contractions and cervical change) may affect the likelihood of adverse respiratory outcomes.[10] Like preeclampsia, there are a number of potential maternal medical conditions that can contribute to the development of specific respiratory morbidities; respiratory distress syndrome and bronchopulmonary dysplasia (BPD) are 2 examples of adverse respiratory outcomes that have been widely studied.[13,17] For example, in some circumstances, exposure to intrauterine inflammation in the form of chorioamnionitis may induce lung maturation and

favorable respiratory outcomes, while in other circumstances, the same insult may cause acute lung inflammation and injury, resulting in severe BPD.[13] The reasons for this variable response are unknown but are likely due to a complex interplay of oxygen exposures, nutrition, and exposure to other postnatal supportive interventions, which can affect BPD. In other studies, intrapartum chorioamnionitis has been associated with an increased risk for childhood asthma.[14] Babies who are growth restricted or small for gestational age are also at elevated risk for developing both respiratory distress syndrome and BPD.[15,16] Clear definitions of fetal growth restriction and gestational age are important for newborn assessment and classification. Finally, it is not unexpected that preeclampsia is also independently associated with an elevated risk for BPD, given that this pregnancy complication is closely related to early onset and severe fetal growth restriction in many situations, and both conditions seem to have placental origins.[17] Indeed, abnormal placental histopathology indicating maternal vascular underperfusion has been associated with the development of BPD.[18]

One additional challenge when investigating the effect of the prenatal period on fetal lung development is the inability to directly study the fetal human lung. Animal models in combination with surrogate markers of lung injury (eg, vascular endothelial growth factor and soluble fms-like tyrosine kinase-1) from maternal blood, amniotic fluid, and/or the placenta may provide viable alternative investigative strategies.[19,20]

Developmental Programming and Lung Development

Recently, significant attention across multiple disciplines and organ systems has focused on the importance of the microbiome in determining health and disease and the importance of these microbes in developmental programming. The respiratory system is no exception. A unique steady-state microbiota exists in the lungs, and colonization of the airways provides crucial signals for local immune cell maturation.[21] Microbial exposure from the interaction of the maternal-placental-fetal unit, the route of birth, or even intestinal microbiota can alter the collective genome of the lung microbiota and shape lung trajectory toward or away from disease later in life.[22]

The placenta is no longer considered a sterile organ, and the effect of maternal-fetal microbiomes on long-term respiratory outcomes is an area of ongoing investigation.[23-25] In animal models, modest lung airway and vascular injuries are induced by chorioamnionitis, and this injury is directly and indirectly linked to lung development and growth pathways.[13,23] Under normal circumstances, bacteria establish clinically occult reservoirs in the maternal-placental-fetal interface, which harbors a unique microbiome composed of "housekeeping" or nonpathogenic microbiota.[24,25] The placenta can house these microbes and prevent them from mounting an immune response that could lead to adverse pregnancy or fetal outcomes. Thus, the balance of housekeeping and pathogenic microorganisms, rather than the absolute presence of any microbes, is key in determining the development of disease. Although the modulation of inflammation at the maternal-fetal interface is likely an important driver of fetal outcomes, the mechanisms are largely unknown.

Microorganisms from the gut can also influence the lung microbiome. Animal studies have suggested an association between gut microbiota, immune regulation, and lung health, recently termed the *gut-lung axis*.[22] Marsland and Gollwitzer[22] demonstrated in a mouse model that early life multibacterial stimuli in the gut altered a variety of cellular mediators of pulmonary immunity. Although there is ongoing work in humans to evaluate associations between the identity of specific enteric microbiome signatures and lung development in premature infants, limited studies exist on term and late preterm infants.[26] Although composition of the intestinal microbiota stabilizes with age, there may be a simultaneous seeding of lung and intestinal microbiota during the critical window of lung development, and several factors, such as antibiotic therapy, infectious agents, and nutritional supplements, may also modulate the airway microbiota.[22]

In addition to the microbiome, maternal nutrition is a significant contributor to developmental programming and lung development. Maternal diet during pregnancy modulates healthy lung development and mediates disease susceptibility. The Barker[27] hypothesis proposes that fetal undernutrition in middle to late gestation leads to disproportionate fetal growth and induces permanent changes in body structure. Indeed, protein deprivation during pregnancy increases bronchial reactivity in human studies[28] and leads to sustained impairment of alveolarization in animal models.[29] In contrast, maternal high-fat diet exposure in utero induces an aggravated inflammatory cell recruitment effect in the fetal lung and promotes lung tissue remodeling in rat models.[30] Evidence is also accumulating that both maternal nutrition prior to and at conception and environmental factors during early life have long-term effects on later health outcomes; these processes likely reflect developmental programming responses to periconceptional exposures.[31]

Environmental Interactions and Exposures

There are multiple opportunities during the antenatal and immediate postnatal periods for environmental exposures that may directly or indirectly influence lung health outcomes among infants born at any gestational age. These include maternal gestational diabetes mellitus, medication or drug exposure during pregnancy, peripartum infection, cesarean delivery (with possible resultant effect on the diversity of the lung microbiome), postnatal exposure to oxygen, and postnatal initiation of positive pressure ventilation.

One well-studied exposure is cigarette smoke, which has significant effects on developing lungs. Antenatal exposure (irrespective of postnatal exposure) doubles the risk of childhood asthma, increases the risk for sudden infant death syndrome, thickens airways and vascular walls, and may permanently alter alveolar and airway geometry.[32,33] Maternal smoking may lead to a lifelong decrease in forced expiratory flows, with changes into adulthood. Animal and human studies suggest that vitamin C supplementation (an antioxidant) provided to maternal smokers during pregnancy may block some in utero effects of nicotine and improve lung function among newborn infants.[32,33] However, the long-term effects of this supplementation are largely unknown. This is a prime example of how one adverse environmental exposure can be potentially abrogated by an additional positive exposure.

Other studies examining the effects of various vitamin supplements during pregnancy and early childhood on lung function have had mixed results. To our knowledge, there are few studies of vitamin supplementation of pregnant women related to lung health in offspring and even fewer of pregnant smokers. Vitamin A is thought to regulate lung growth through cell proliferation and differentiation; improved lung function was observed among offspring when undernourished pregnant women received vitamin A supplementation.[34] In an experimental animal model, maternal vitamin D deficiency increased offspring airway smooth muscle mass, baseline airway resistance, inflammation, and altered postnatal lung structure and function, suggesting a critical window for vitamin D replacement.[35] Similarly in humans, vitamin D deficiency during in utero lung development resulted in decreased forced vital capacity z scores in childhood and early adolescence.[36] Reduced vitamin E levels in maternal blood in the first and second trimesters among infants with intrauterine growth restriction was associated with reduced lung function at 5 years of age and an increased risk of asthma.[37] Thus, the optimal doses of vitamin supplementations may need to be reexamined, particularly during pregnancy. Doubts regarding the optimal level of nutrients, the ideal source of supplementation (from food vs pills), and the best timing to provide the supplementation (prenatal, postnatal, or both) abound. It is also unclear whether individuals who are nutrient replete need supplementation.

The mechanisms by which these positive (eg, vitamin exposure) and negative (eg, nicotine) environmental stimuli influence lung development are incompletely understood. Basic science research has attempted to investigate the underlying causative mechanisms by which these exposures alter the normal course of development. Epigenetic changes in gene expression can explain phenotypic variation caused by environmental factors. Therefore, epigenetic analysis may provide clues to the potential etiologies behind human disease, including lung disease. Both developmental (patterns of gene expression independent of the environment) and environmental (patterns of gene expression that vary depending on the environment) epigenetics can affect the regulation of transcription and can also affect noncoding regions of the genome. While studies have suggested a role for epigenetics in nearly all disease processes, most research has demonstrated only association, not causation. Additional work is needed to determine the underpinnings of disease at the molecular level and the influence of environmental exposures on gene expression, which may lead to new therapeutic strategies.

Conclusions and Final Recommendations

There are multiple opportunities to address the specific research priorities outlined in the Table. It is clear that future investigations will need not only to examine abnormal lung development, but also to use developing technology and resources to better define normal. Some proportion of future studies will need to use birth cohorts to capture the important influence of preconception and obstetric risk factors on lung health, development, and disease. It is imperative that these birth cohorts include well-characterized obstetrical data, with comprehensive plans for prospective follow-up. On the other hand, the importance of continued basic science, translational, and animal studies cannot be overemphasized, particularly as these data may provide more immediate answers regarding causality. Multidisciplinary approaches with obstetricians, neonatologists, pediatric and adult pulmonologists, epidemiologists, and basic scientists are essential for the comprehensive research needed to advance the understanding of lung development across a lifetime.

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