Third, we as a community must move beyond convenience cohorts to carefully planned cohorts, taking into account the diversity parameters mentioned above. Finally, a minimum set of metadata must be defined for human samples. It is possible that integrating this data set with currently available normal human lung and airway data sets (3, 7, 10, 11) as well the recent very large human lung disease data sets (6, 8, 12, 13) will allow immediate validation and augmentation of the exciting results in this manuscript. In summary, the study by Deprez and colleagues is a major milestone toward the generation of a comprehensive cell atlas of the human airway. Providing such a comprehensive and accurate atlas will improve our understanding of the airway and its function in development, health, and disease. Combining this effort with similar efforts from diseased tissues will eventually lead to better approaches in the diagnosis and management of airway diseases. ■

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

Jonas Christian Schupp, M.D.
Section of Pulmonary, Critical Care and Sleep Medicine
Yale University School of Medicine
New Haven, Connecticut

Xiting Yan, Ph.D.
Section of Pulmonary, Critical Care and Sleep Medicine
Yale University School of Medicine
New Haven, Connecticut
and
Department of Biostatistics
Yale School of Public Health
New Haven, Connecticut

Naftali Kaminski, M.D.
Section of Pulmonary, Critical Care and Sleep Medicine
Yale University School of Medicine
New Haven, Connecticut

ORCID ID: 0000-0002-7714-8076 (J.C.S.).

References

1. Schiller HB, Montoro DT, Simon LM, Rawlins EL, Meyer KB, Strunz M, *et al*. The human lung cell atlas: a high-resolution reference map of the human lung in health and disease. *Am J Respir Cell Mol Biol* 2019;61: 31–41.
2. Muus C, Luecken MD, Eraslan G, Waghray A, Heimberg G, Sikkema L, *et al*. Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlights inflammatory programs in putative target cells [preprint]. *bioRxiv*; 2020 [accessed 2020 Apr 20]. Available from: www.biorxiv.org/content/10.1101/2020.04.19.049254v1.
3. Deprez M, Zaragosi L-E, Truchi M, Becavin C, Ruiz García S, Arguel M-J, *et al*. A single-cell atlas of the human healthy airways. *Am J Respir Crit Care Med* 2020;202:1636–1645.
4. Montoro DT, Haber AL, Biton M, Vinarsky V, Lin B, Birket SE, *et al*. A revised airway epithelial hierarchy includes CFTR-expressing ionocytes. *Nature* 2018;560:319–324.
5. Plasschaert LW, Žilionis R, Choo-Wing R, Savova V, Knehr J, Roma G, *et al*. A single-cell atlas of the airway epithelium reveals the CFTR-rich pulmonary ionocyte. *Nature* 2018;560:377–381.
6. Vieira Braga FA, Kar G, Berg M, Carpaij OA, Polanski K, Simon LM, *et al*. A cellular census of human lungs identifies novel cell states in health and in asthma. *Nat Med* 2019;25:1153–1163.
7. Goldfarbmuren KC, Jackson ND, Sajuthi SP, Dyjack N, Li KS, Rios CL, *et al*. Dissecting the cellular specificity of smoking effects and reconstructing lineages in the human airway epithelium. *Nat Commun* 2020;11:2485.
8. Adams TS, Schupp JC, Poli S, Ayaub EA, Neumark N, Ahangari F, *et al*. Single-cell RNA-seq reveals ectopic and aberrant lung-resident cell populations in idiopathic pulmonary fibrosis. *Sci Adv* [online ahead of print] 8 Jul 2020; DOI: 10.1126/sciadv.aba1983.
9. Kicic A, de Jong E, Ling K-M, Nichol K, Anderson D, Wark PAB, *et al*.; WAERP; AusREC. Assessing the unified airway hypothesis in children via transcriptional profiling of the airway epithelium. *J Allergy Clin Immunol* 2020;145:1562–1573.
10. Travaglini KJ, Nabhan AN, Penland L, Sinha R, Gillich A, Sit RV, *et al*. A molecular cell atlas of the human lung from single cell RNA sequencing [preprint]. *bioRxiv*; 2020 [accessed 2019 Aug 27]. Available from: https://www.biorxiv.org/content/10.1101/742320v1.
11. Raredon MSB, Adams TS, Suhail Y, Schupp JC, Poli S, Neumark N, *et al*. Single-cell connectomic analysis of adult mammalian lungs. *Sci Adv* 2019;5:eaaw3851.
12. Habermann AC, Gutierrez AJ, Bui LT, Yahn SL, Winters NI, Calvi CL, *et al*. Single-cell RNA sequencing reveals profibrotic roles of distinct epithelial and mesenchymal lineages in pulmonary fibrosis. *Sci Adv* [online ahead of print] 8 Jul 2020; DOI: 10.1126/sciadv.aba1972.
13. Reyfman PA, Walter JM, Joshi N, Anekalla KR, McQuattie-Pimentel AC, Chiu S, *et al*. Single-cell transcriptomic analysis of human lung provides insights into the pathobiology of pulmonary fibrosis. *Am J Respir Crit Care Med* 2019;199:1517–1536.

Birth Cohort Studies: Their Next Coming of Age

The fetus was traditionally considered to have a privileged place *in utero*, where it was protected from harmful environmental exposures. The paradigm that we are all born in a state of good health was challenged by research in the 1980s and 1990s that demonstrated links between reduced birth weight and increased risk for noncommunicable diseases (NCDs) in later life. The paradigm that antenatal exposures can have lifelong implications for health and well-being is now well accepted (1).

Inspired by the concept of "fetal origins of disease" and later concepts such as developmental plasticity and predictive adaptive responses, recruitment began in the 1980s to birth cohort studies designed to give insight into the premorbid physiological mechanisms linking the antenatal environment to later NCDs. To

Originally Published in Press as DOI: 10.1164/rccm.202007-2808ED on August 11, 2020

obtain an early return from their investment in time and effort, investigators explored NCD outcomes in childhood (not adulthood), and the focus of their cohorts was asthma, which was reaching an "epidemic" prevalence at that time.

The TCRS (Tucson Children's Respiratory Study) was at the vanguard of these birth cohort studies and recruited 1,246 infants between 1980 and 1984. Infant lung function was measured during tidal breathing using recently described methodologies, and the outcomes included FRC, $\dot{V}$max at FRC ($\dot{V}$maxFRC), and the time to peak expiration:total expiration (t_{PTEF}/t_E) ratio. Testing was completed in 376 infants, including 180 who were assessed before 6 months of age. Generous doses of chloral hydrate were used to induce sleep, and investigators doing the time-consuming testing might reasonably have wondered whether the measurements they were taking would add up to much.

They need not have worried. The first publication reported an association between reduced $\dot{V}$maxFRC and wheeze among the 120 participants who were symptom free when tested at a mean age of 2 months (2). A further publication, which has been cited more than 4,000 times, found that the association between reduced $\dot{V}$maxFRC and wheeze was only transient (3). Other cohorts of similar design found reduced $\dot{V}$max FRC (4, 5) and t_{PTEF}/t_E (6) and other abnormalities of pulmonary physiology (7) were associated with persistent wheeze or asthma, with reduced lung function persisting in some individuals from infancy through to later life (8, 9). In a paper published in this issue of the *Journal*, the TCRS team (pp. 1646–1655) confirm a persisting relationship between both reduced $\dot{V}$maxFRC and t_{PTEF}/t_E and asthma (10).

The latest paper from the TCRS team uses questionnaire data collected at 12 times between the ages of 6 and 32 years and applies longitudinal analyses, including a survival analysis, to the relationship between infant lung function and active asthma in later life (10). Individually, reduced $\dot{V}$maxFRC and t_{PTEF}/t_E were associated with increased risk for asthma, and new onset asthma continued to occur into the third decade. In combination, reduced $\dot{V}$maxFRC and t_{PTEF}/t_E before 8 weeks of age had a threefold increased risk for asthma by the age of 36 years. Childhood asthma has many associated risk factors with odds ratios between 1.5 and 2.0, and a ratio of 3.0 suggests that early-life lung function is an important trait relative to the many described genetic and environmental factors.

In a second tantalizing set of results in their paper, the TCRS team present a series of comparisons between infant lung function and high-resolution computed tomography in 38 individuals aged 26 years (10). Among this subset of individuals, reduced t_{PTEF}/t_E was associated with reduced airway wall thickness and airway caliber. These proof-of-concept results might indicate that the structural airway changes associated with asthma are already in place by the first few months of life. Excitement for these findings needs to be tempered by the apparent inconsistencies with data from the TCRS and elsewhere. If t_{PTEF}/t_E is truly related to structural lung changes, there should be an association with spirometry; $\dot{V}$maxFRC, but not t_{PTEF}/t_E, was associated with spirometry at 26 years of age. If structural changes are present in early life, they should be present on airway biopsies, but no such evidence was seen in a Finnish cohort of wheezy infants with reversible airway obstruction (11). Although replication of these findings is clearly needed, there is a challenge in tracking down the few thousand 26-year-olds on the planet for whom infant lung function data are available.

The take-home message from this article (10) is that processes that determine respiratory physiology and asthma risk into the fourth decade of life are present in early infancy and are likely active *in utero*. The usual limitations of birth cohort studies apply to TCRS and include recruitment bias, bias in follow-up (a relatively high proportion [36%] of participants had active asthma by 36 yr of age), and loss to follow-up. An additional limitation is that because the environment and lifestyles have changed since the early 1980s, these results may not be generalizable to individuals conceived in the early 2020s.

Where do we go from here? Can we screen for asthma with infant lung function testing? Unfortunately, we remain an impossibly long way from considering screening for asthma by infant lung function; testing lacks sensitivity and specificity, and we know that reduced infant lung function resolves in many individuals (12). Can we improve infant lung function when it is found to be reduced? Diet may help by preventing excessive weight gain in infancy, and vitamin C treatment during pregnancy may possibly soften the blow to infants' lungs from exposure to maternal smoking (13). What we collectively can do is to carry on advocating a healthy lifestyle and "lived environment" for everyone, especially pregnant mothers.

Extended follow-up of cohorts has demonstrated that in many individuals, children do not grow out of asthma; symptoms merely go into a temporary remission. Childhood asthma is a risk factor for chronic obstructive pulmonary disease (14). Taking a step back from the early origins of asthma/chronic obstructive pulmonary disease, what is clear from birth cohorts recruited in the United Kingdom in the 1950s (where less antenatal data are available) is that there are early origins of many other common NCDs in the older population, including ischemic heart disease, chronic renal failure, and even dementia (15). The next generation of researchers is now slowly taking over the reins of birth cohorts, such as TCRS, from the colleagues who founded them. Over the coming years, as this new generation of researchers ventures forth, the birth cohorts recruited in the 1980s will enter a new age in which they will continue to yield insight into respiratory NCDs and also start shining light on pathways to some nonrespiratory NCDs. ■

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

Steve Turner, M.D.
Child Health
University of Aberdeen
Aberdeen, United Kingdom

ORCID ID: 0000-0001-8393-5060 (S.T.).

References

1. Hoffman DJ, Reynolds RM, Hardy DB. Developmental origins of health and disease: current knowledge and potential mechanisms. *Nutr Rev* 2017;75:951–970.
2. Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med* 1988;319:1112–1117.
3. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ; The Group Health Medical Associates. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133–138.

4. Mullane D, Turner SW, Cox DW, Goldblatt J, Landau LI, le Souëf PN. Reduced infant lung function, active smoking, and wheeze in 18-year-old individuals. *JAMA Pediatr* 2013;167:368–373.
5. Bisgaard H, Jensen SM, Bønnelykke K. Interaction between asthma and lung function growth in early life. *Am J Respir Crit Care Med* 2012;185: 1183–1189.
6. Håland G, Carlsen KC, Sandvik L, Devulapalli CS, Munthe-Kaas MC, Pettersen M, *et al*.; ORAACLE. Reduced lung function at birth and the risk of asthma at 10 years of age. *N Engl J Med* 2006;355: 1682–1689.
7. van der Gugten AC, Uiterwaal CSPM, van Putte-Katier N, Koopman M, Verheij TJM, van der Ent CK. Reduced neonatal lung function and wheezing illnesses during the first 5 years of life. *Eur Respir J* 2013;42: 107–115.
8. Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet* 2007;370:758–764.
9. Turner S, Fielding S, Mullane D, Cox DW, Goldblatt J, Landau L, *et al*. A longitudinal study of lung function from 1 month to 18 years of age. *Thorax* 2014;69:1015–1020.
10. Guerra S, Lombardi E, Stern DA, Sherrill DL, Gilbertson-Dahdal D, Wheatley-Guy CM, *et al*. Fetal origins of asthma: a longitudinal study from birth to age 36 years. *Am J Respir Crit Care Med* 2020;202: 1646–1655.
11. Belgrave DCM, Granell R, Turner SW, Curtin JA, Buchan IE, Le Souëf PN, *et al*. Lung function trajectories from pre-school age to adulthood and their associations with early life factors: a retrospective analysis of three population-based birth cohort studies. *Lancet Respir Med* 2018;6:526–534.
12. McEvoy CT, Shorey-Kendrick LE, Milner K, Schilling D, Tiller C, Vuylsteke B, *et al*. Oral vitamin C (500 mg/d) to pregnant smokers improves infant airway function at 3 Months (VCSIP): a randomized trial. *Am J Respir Crit Care Med* 2019;199: 1139–1147.
13. Tagiyeva N, Devereux G, Fielding S, Turner S, Douglas G. Outcomes of childhood asthma and wheezy bronchitis: a 50-year cohort study. *Am J Respir Crit Care Med* 2016;193:23–30.
14. Saglani S, Malmström K, Pelkonen AS, Malmberg LP, Lindahl H, Kajosaari M, *et al*. Airway remodeling and inflammation in symptomatic infants with reversible airflow obstruction. *Am J Respir Crit Care Med* 2005;171:722–727.
15. Staff RT, Hogan MJ, Whalley LJ. The influence of childhood intelligence, social class, education and social mobility on memory and memory decline in late life. *Age Ageing* 2018;47: 847–852.

COVID-19 and Interstitial Lung Disease: Keep Them Separate

Since the emergence of the novel coronavirus now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019, there have been more than 50 million documented infections and 1.2 million deaths worldwide (1). Our understanding of SARS-CoV-2 transmission and pathogenicity and the mechanism by which it causes coronavirus disease (COVID-19) has evolved rapidly, as have the recommendations on treatment and risk mitigation strategies. The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic to severe disease necessitating ICU admission and mechanical ventilation (2). Up to 45% of those infected are asymptomatic, whereas approximately 3–10% require hospitalization (3–5). Severe disease, defined by dyspnea, hypoxemia, and pulmonary infiltrates, occurs in up to 20% of hospitalized patients and is associated with a high mortality rate (6). However, these estimates vary widely depending on the population being studied. Advanced age, male sex, and multiple comorbidities all increase the risk of death from COVID-19 (7). A key component of the public health response to COVID-19 has been a focus on identifying groups at increased risk for complications and death from COVID-19 and reducing their risk of exposure to SARS-CoV-2.

Interstitial lung disease (ILD) is characterized by injury to the alveolar epithelium and abnormal wound healing (8). Patients with ILD have diminished pulmonary reserve and impaired gas exchange. Viral infections can trigger acute exacerbations, which are associated with poor outcomes (9). Many patients with ILD are on immunosuppressive medications. It stands to reason that patients with ILD would have an increased rate of complications and death from COVID-19. However, until now, no studies have examined the impact of COVID-19 on these patients.

In the current issue of the *Journal*, two manuscripts report on the outcomes of adults with COVID-19 and preexisting ILD. Drake and colleagues (pp. 1656–1665) assess in-hospital mortality of 161 patients with ILD hospitalized with COVID-19 across multiple centers in Europe and compare it with a control group of patients with COVID-19 without underlying lung disease, matched on age, sex, and nonpulmonary comorbidities using a propensity score (10). They find that patients with ILD have significantly higher in-hospital mortality compared with those without ILD (49% vs. 35%). The risk of mortality increases with older age and male sex. For instance, for males over the age of 75, mortality is 62%. The presence of obesity, idiopathic pulmonary fibrosis, and FVC below 80% predicted are also associated with greater risk of death.

Esposito and colleagues (pp. 1710–1713) examine mortality among 46 patients with preexisting ILD diagnosed with COVID-19 at six Boston medical centers and compare it with age-, sex-, and race-matched controls without ILD evaluated at the same hospitals (11). Mortality in this study is 33% for patients with ILD, compared with 13% for controls. After adjustment for age, sex, race, smoking status, comorbid cardiovascular disease, and use of immunosuppression, patients with ILD were found to have a more than fourfold higher risk of dying compared with controls. In contrast to Drake and colleagues, this study included both hospitalized and nonhospitalized patients. Adults with ILD were more likely to be admitted to the hospital (74% vs. 58%) and require ICU care (47% vs. 23%) and less likely to be discharged

Originally Published in Press as DOI: 10.1164/rccm.202010-3918ED on October 28, 2020